

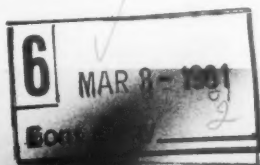
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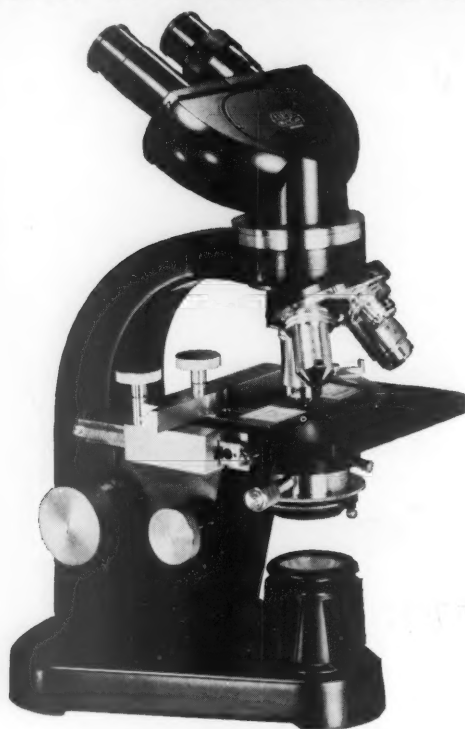
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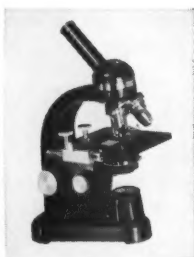


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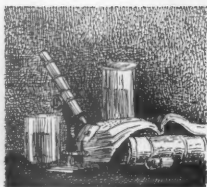
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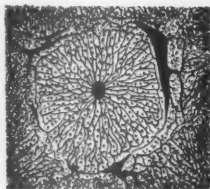
IT HAPPENED THIS MONTH...

a glance at yesterday in relation to today



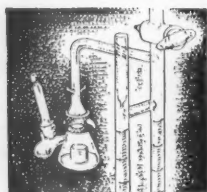
IN MARCH—(1884)—*Science* reviews a Brazilian pamphlet on the genesis of beriberi. Dr. J. B. DeLacerda cultured blood of beriberi patients in meat solution and obtained a microphyte similar to the "bacillus of carbuncle". Animals infected with this organism succumb to paralytic disease in 5 to 20 days. The microphyte was then recovered from the muscles and spinal medulla. "From these facts the author draws the logical conclusion, that beriberi is a parasitic disease, and that the parasites attack particularly the blood, muscles, and medulla."¹

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IN MARCH—(1949)—Otto Meyerhof publishes another of his interesting papers in the field of carbohydrate metabolism. Previous studies had shown that large amounts of phosphorylated hexoses are required to maintain steady continuous glycolysis in homogenates or centrifuged extracts of malignant tumors. In the absence of such phosphate donors, continuous glucose utilization can occur only if the activity of ATPase (in terms of phosphate turnover) is twice that of hexokinase. Meyerhof and Wilson³ show that enzymatic balance may be obtained by adding yeast hexokinase or inhibiting the activity of the tumor ATPase.

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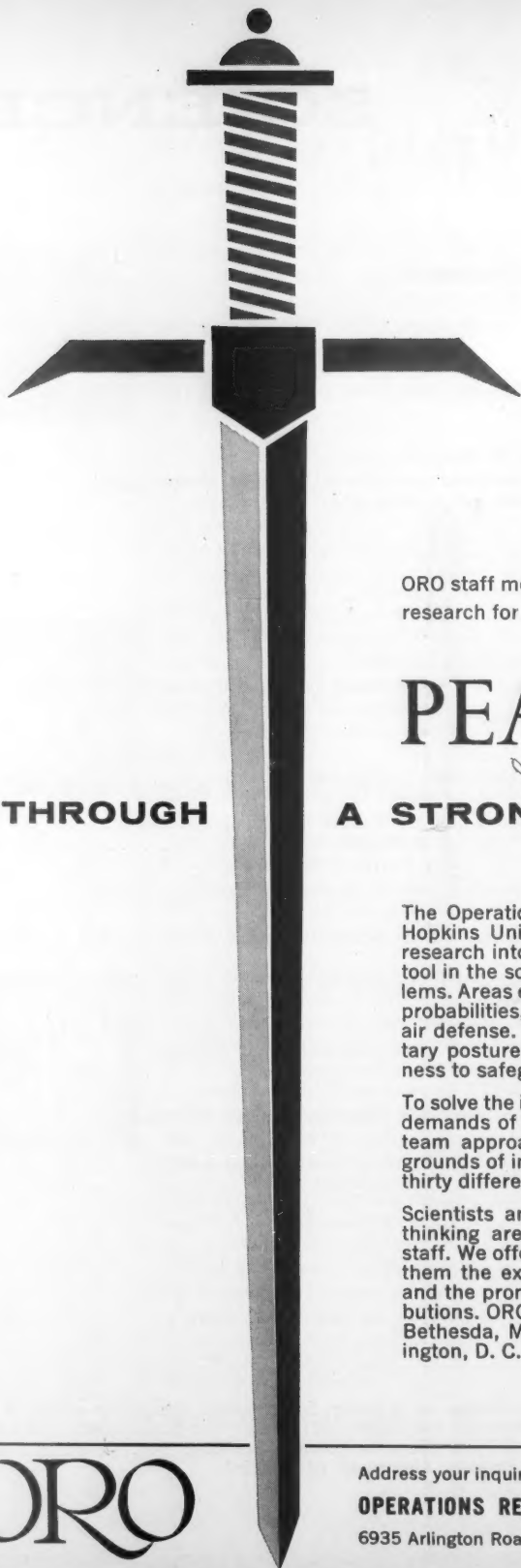
1. (Review): The bacillus of beriberi. *Science* 3:331 (March 14) 1884. 2. Hopkins, F. C.: On an autoridisable constituent of the cell. *Biochem J.* 15:286 (1921). 3. Meyerhof, O. and Wilson, J. R.: Studies on the enzymatic system of tumor glycolysis. I. Glycolysis of free sugar in homogenates and extracts of transplanted rat sarcoma. *Arch. Biochem.* 21:1 (March) 1949.



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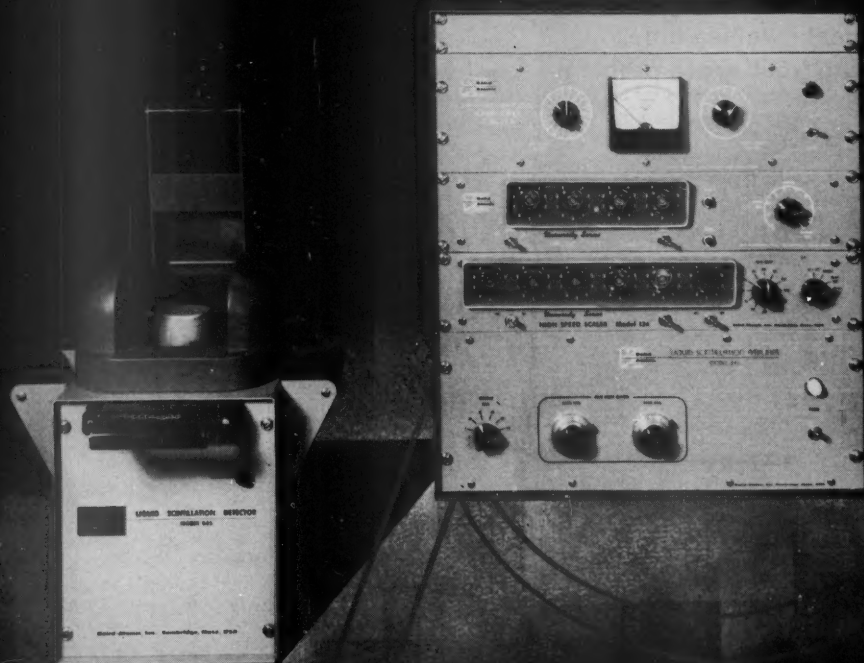
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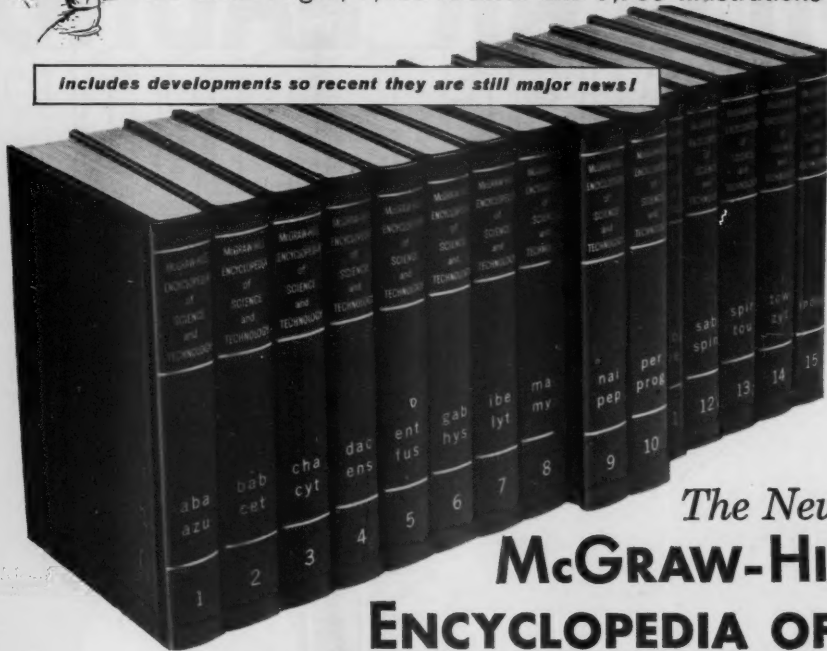
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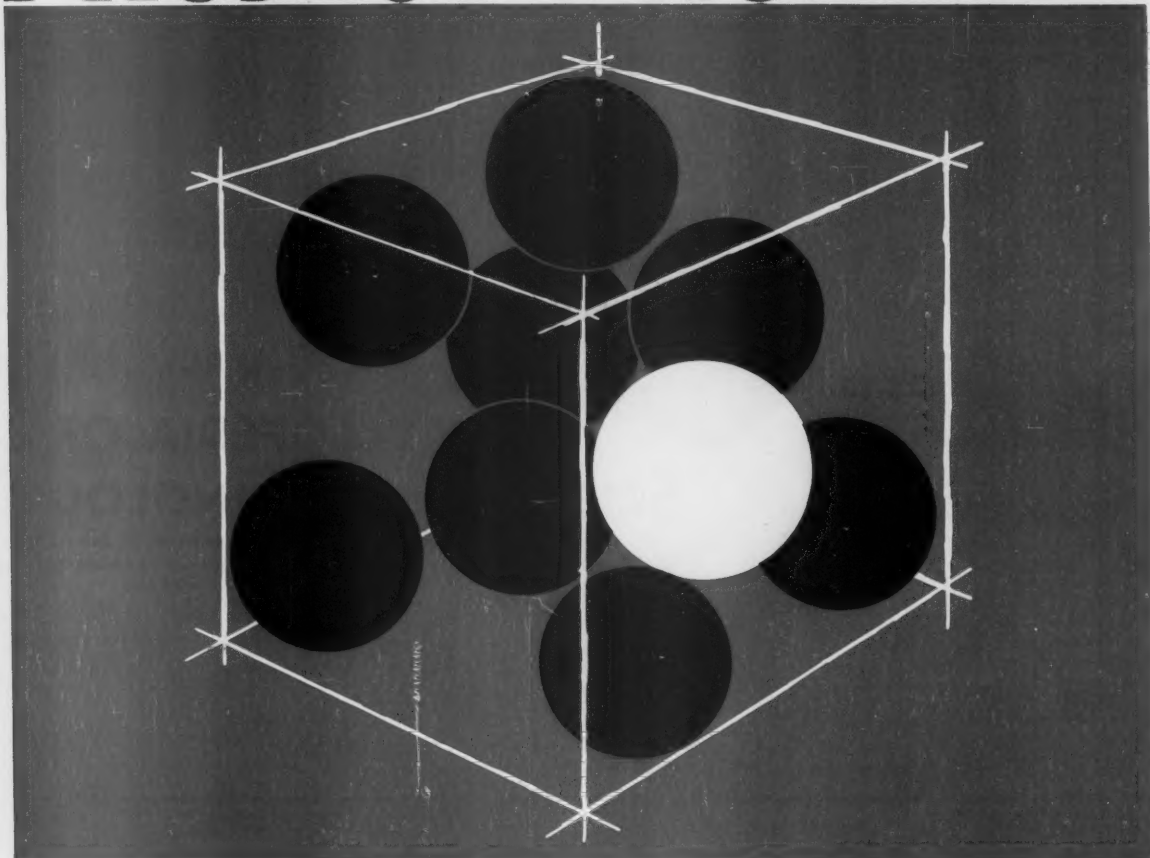
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Electricity and Personal Magnetism

We are puzzled in one respect by a recent series of advertisements in which Arthur Schlesinger, Jr., John Mason Brown, and Edward Teller endorse a 54-volume set of writings called the "Great Books of the Western World." The set of writings is published by Encyclopaedia Britannica in collaboration with the University of Chicago. It is supposed to put the thinking person in touch with the great ideas of civilization by making available to him, in their entirety, great works by the great thinkers themselves. Now the set, which can be bought on easy budget terms, includes some science. It includes, for example, Faraday's *Experimental Researches in Electricity*, which is 642 pages long, two columns to a page. What puzzles us is whether such learned and astute public figures really believe that a person interested in gaining an understanding of modern science and its development should proceed by making his way through this material.

To be sure, the reader is permitted at his discretion to skip unprofitable pages, and few thinking persons are likely to linger very long over, say, tables giving, for the 1840's, monthly magnetic declinations at Toronto, St. Petersburg, Washington, Lake Athabasca, and Fort Simpson. But how helpful, in addition, if the reader were only told which portions of the work describe fundamental discoveries and which of Faraday's views are no longer accepted. And how helpful to be told, if the readers of this material are to communicate with anybody but one another, which of Faraday's special terms have been replaced by other expressions and what the new expressions are. And finally, how helpful to be advised how much of this work to read before turning to other writings of Faraday, to other 19th century scientists, and to other scientists of other centuries.

Putting aside for the moment the problem of the general reader, our own impression is that a professional scholar, who is not a physicist or a historian of science, would be delighted, when reading Faraday, to supplement his own judgment on how he could concentrate his efforts with the judgment of some better informed colleagues. He would regard such assistance as no more presumptuous than the suggestion that he read Faraday in the first place. After all, the material may be new to him, but it is not new to the world. Why, then, should more heroic demands be made of the general reader than of the professional scholar? Furnishing each reader with a host of learned friends may not be feasible, but it is possible to give each one, in the form of properly introduced and annotated texts, the information such friends could supply. This is not to say that the general reader cannot improve his understanding of modern science and its development by studying great scientific papers. And there may even be a grain of truth in the advertisements' claim that perusal of man's great intellectual achievements will enable the reader "to think, speak, and act with new and impressive weight." But if contact with the soil is good on occasion for everyone, it does not follow that everyone must plow the soil afresh.

Other readers of these advertisements, of course, may be puzzled in other respects. Admirers of Dostoevski, for example, will note that the set of writings does include a reading schedule for some, if not all, of the books, and that the first half of *The Brothers Karamazov* is scheduled for one year, and the second half for the following year. What may puzzle Dostoevski enthusiasts is whether Schlesinger, Brown, and Teller are really so unfeeling as to ask any reader of the first half of the novel to wait even a week before starting the second half.—J.T.



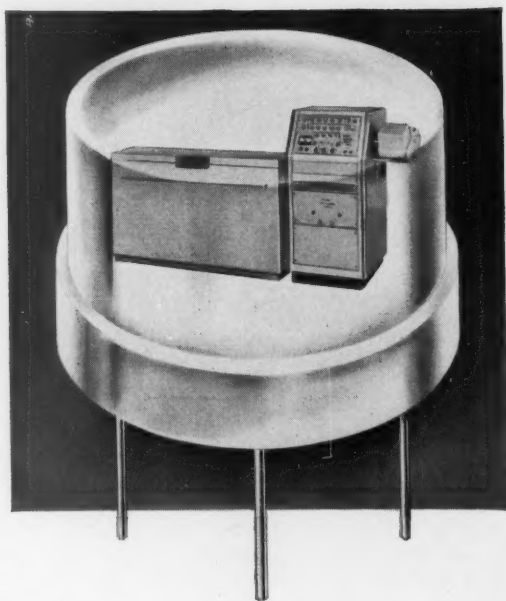
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This undeveloped field provides broad possibilities in experimental and applied therapeutics.

Robert Gaunt, J. J. Chart, A. A. Renzi

The search for drugs to treat the ills of mankind is almost as old as the ills themselves. Modern applied pharmacology is a sophisticated extension of ancient practice. In addition to their use in the treatment of infectious diseases, it is customary to prescribe drugs to modify the function or dysfunction of the nervous, cardiovascular, respiratory, gastrointestinal, or renal systems. With the well-known exceptions of the anti-thyroid drugs, however, chemical agents foreign to the human body had, until very recently, virtually no established uses in regulating the manifold activities or diseases of the endocrine glands. The use of isolated secretions of endocrine glands—that is, hormones—in their natural or chemically modified state to treat disease is of course a common and useful practice. What has been strangely lacking, however, is a well-developed endocrine pharmacology involving knowledge and use of chemical nonhormonal compounds which can alter the secretion or action of hormones. The potentialities of this approach are particularly well illustrated by that large battery of drugs which, with a high and selective specificity, can block particular functions of the autonomic nervous system. This high-water mark in pharmacological achievement involves interference with the production or action of neurohumoral substances. Analogous possibilities exist in so far as the humors

of the endocrine glands proper are concerned.

One reason for the limited advance in this field has been lack of concentrated, systematic effort. This in turn is due to the fact that the classic approaches to endocrinology have been spectacularly successful in the last few decades and that preoccupation with them preempted the time and energy of the students of this science. This classic approach has involved the following three phases, all of which have been, and still continue to be, productive.

1) *The identification, isolation, and synthesis of hormones and their therapeutic use in analogous deficiency syndromes.* This represents the first and self-evident approach to endocrine problems. Its prosecution has resulted in substitution therapies for diabetes mellitus, Addison's disease, myxedema, the menopausal syndrome, and many other disorders.

2) *The chemical modification of hormones to potentiate or prolong their activity.* Few hormones are now administered to patients in the natural state in which presumably they are released by the endocrine glands into the blood stream. Slight chemical modification of the natural compound may delay its rate of absorption from an injection site or delay its metabolic degradation in the body, or both, with the result that the frequency of administration

can be greatly reduced. Hence we prescribe long-acting insulins, esters instead of the free alcohols of the steroid hormones, and so on. Similarly, slight chemical modification may inhibit the destruction of a hormone in the gastrointestinal tract and thus make its oral administration feasible and economical. Examples of this are the oral use of methyltestosterone instead of the natural testosterone and of ethinyl estradiol instead of estradiol. Such pharmaceutical manipulations, however, were not designed or intended to alter the biological activity of the hormone molecule but only to extend, enhance, and conserve it.

In one instance, that of stilbestrol and its derivatives, compounds which differ greatly from the natural estrogens produce effects essentially identical to those of the natural estrogenic hormones (1). Analogous substitutes for other types of hormones are not known to exist.

3) *The chemical modification of hormone molecules to alter their natural activity.* New developments of this type were introduced by the discovery of Fried (2) that 9 α -halogenation of the adrenal cortical hormone, hydrocortisone, resulted in major alterations in the pattern of its biological activity. This has resulted in a flood tide of work (not to be reviewed here) in which chemically and biologically modified hormones have emerged from test tubes in profusion. It is now clear that chemical alteration of steroid hormone molecules can result in an accentuation of one biological activity and diminution of another. The same is apparently true of the polypeptide hormones (3). This makes it possible, both theoretically and in practice, to synthesize hormone-like substances with tailor-made properties to serve specific therapeutic or experimental needs. The most widely used

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substances of this type are the prednisolones and their successors, which are used in treating inflammatory diseases. New ones are surely coming, among them steroids which can control fertility in man (4). It is still true, however, that these chemical alterations of hormone molecules have produced no compounds with fundamentally new properties which were not present to some degree in the parent compounds. It is the ratio and magnitude of the different activities inherent in the parent compounds which have been altered.

Pharmacological Regulation of Endocrine Functions

This brings us to a newer and less well developed approach to the study of endocrinology, which is our main subject—namely, the use of drugs to control endocrine functions. While we are emphasizing here the potential practical applications of such work, any success would also be of equal or greater importance in the theoretical and fundamental studies of the nature of endocrine function. Witness the fruitful use of drugs in the study of neurological phenomena. The work outlined below is of a scattered sort, from many sources. It has seldom received comprehensive attention in the literature. Nevertheless, new work shows that this is a field in which systematic and profitable exploitation will be forthcoming, and one to which an increasing amount of attention will be given.

Theoretically there are many ways in which drugs might modify endocrine function. From a practical standpoint, it would be more useful to have glandular inhibitors rather than stimulants because an excess of hormone usually can be obtained, when needed, by direct administration of the hormone in any quantity. Stated in the form of an outline (amplified below), some of the more obvious routes through which inhibition could be achieved are as follows.

1) A drug might "damage," reversibly or otherwise, the glandular secretory cells which produce hormones—through, for example, alloxan-like action on the pancreas or 1, 1-dichloro-2, 2-bis (*p*-chlorophenyl) ethane-like action on the adrenal (Fig. 1).

2) A drug might inhibit some specific (probably enzymatic) step in the biosynthesis of a hormone—through, for

example, amphenone-like action on the adrenal cortex (Fig. 1).

3) A drug might block the stimulus, however remote, which causes glandular secretory activity—for example, sedative inhibitors of adrenocorticotrophin (ACTH) release (Fig. 1).

4) A drug might block the uptake of an essential raw material for hormone synthesis—for example, the uptake of iodine by the antithyroid drugs.

5) A drug might block the production of an essential precursor to hormone synthesis—for example, inhibitors of cholesterol synthesis which disturb steroid hormone production.

6) A drug might block the reaction of a hormone at a receptor site—for example, the spiro lactone antagonists of aldosterone (Fig. 1).

In some instances it is certain and in others probable that drugs are now known which can and do achieve most of these effects. The fact that, with limited exceptions, they are not widely used is due to the need for better drugs. With the prototypes available, it should be possible to find them.

Drugs Which Inhibit Secretion of Anterior Pituitary Hormones

Work in recent years has clarified considerably the mechanisms by which the secretion of the several hormones of the anterior pituitary is regulated. This is accomplished, first, by the relatively slowly acting "thermostat" or "feedback" mechanism in which the pituitary trophic hormone stimulates secretion of a hormone by the target gland, and the hormone of the target gland in turn acts back to inhibit release of the pituitary trophic hormone. This mechanism operates for most of the pituitary hormones which regulate other endocrine glands—for example, the gonadotrophins, thyrotrophin, and adrenocorticotrophin. It serves as a stabilizing system to prevent violent fluctuations in blood levels of the hormones concerned. There are, however, other regulatory stimuli which can override the feedback system and permit the sudden release of pituitary trophins, presumably to meet immediate or unusual needs. Most regulatory factors apparently operate as follows: neurohumoral cells in the hypothalamus can be stimulated to release or inhibited from releasing from their nerve endings humoral substances which are picked up by the hypothalamico-

hypophyseal portal capillaries and delivered to the anterior pituitary. In the pituitary these neurohumors cause release of pituitary trophins, which in turn stimulate secretion of the target glands (5).

Such mechanisms have been implicated in the release of all anterior pituitary hormones except the growth hormone. The stimuli which impinge upon the hypothalamus to initiate this cycle of events are the subject of much current study and are not well understood. Apparently they may be either neural or blood-borne. Classic examples of their actions, however, are the release of pituitary luteinizing hormone after mating in some mammals and the quick release of adrenocorticotrophin in response to nonspecific stress. In any case, it is evident that a complex chain of events must transpire before the original stimulus (psychic, traumatic, humoral, pharmacological or otherwise) results in secretory response by the target gland involved. Theoretically, blocking of the response might be achieved at any link of the chain by a drug of sufficient specificity; the greater the length of the chain, the greater the vulnerability of the system to pharmacological blockade.

Gonadotrophins. The study of the influence of drugs on the secretion of gonadotrophins was initiated and developed largely by Markee, Everett, and Sawyer (6). They have skillfully used pharmacological tools to great advantage in a long series of studies to reveal important information about fundamental mechanisms in reproductive processes and, incidentally, about the drugs themselves. Thus, it could be shown that the secretion of luteinizing hormone in the rabbit, which causes ovulation under the stimulus of copulation, can be blocked by some (for example, dibenamine) but not all (for example, Regitine) antiadrenergics and by anticholinergics (such as atropine) as well. Studies to determine the time at which drugs had to be given after the stimulus of copulation in order to block ovulation led to the concept that a link blocked by anticholinergic drugs preceded one blocked by antiadrenergics in the presumably complex neural pathways involved.

In the rat, which has a different type of reproductive cycle, the pharmacological relationships were also different. It was possible, however, to block the spontaneously occurring ovulation, pre-

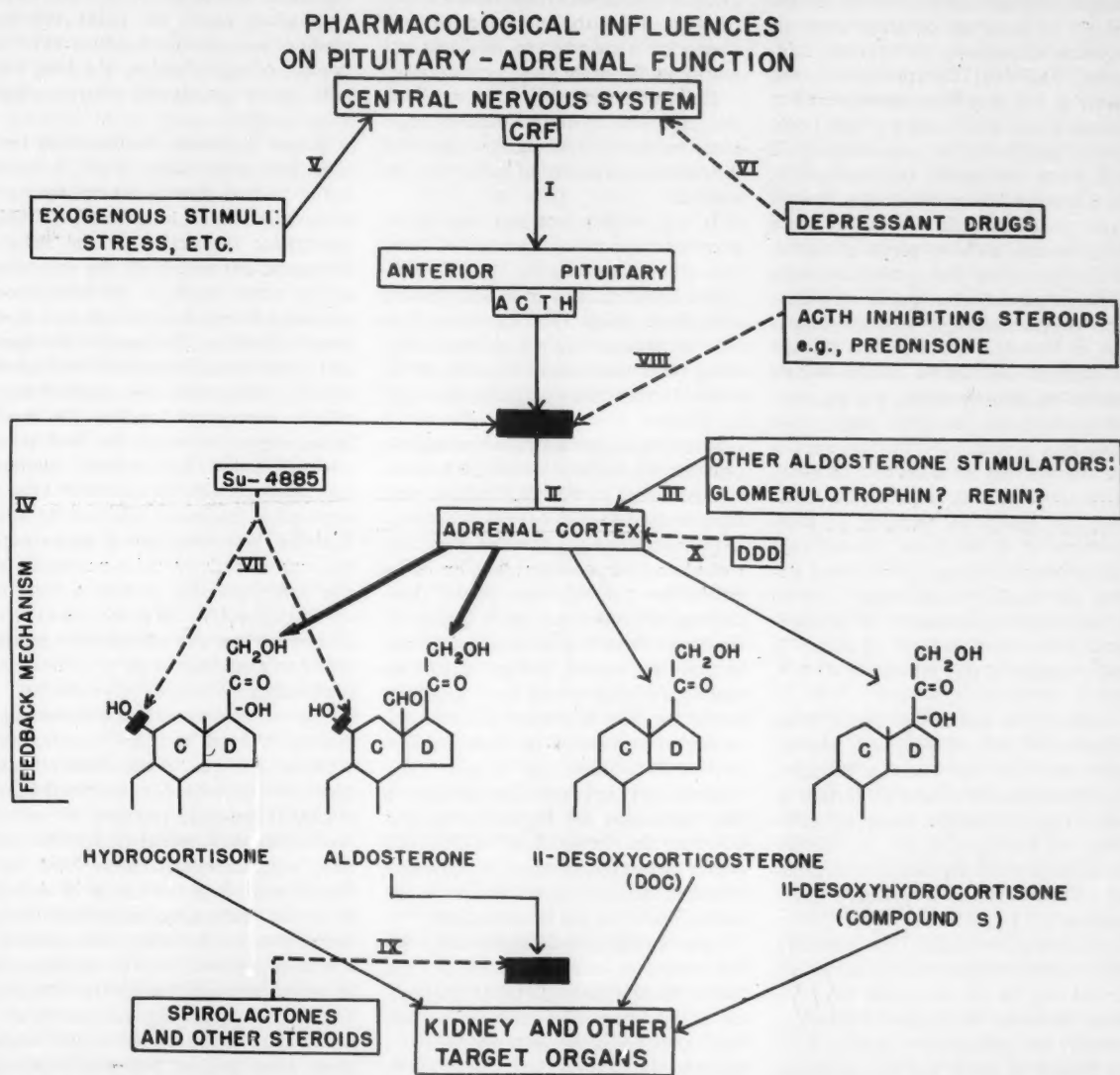


Fig. 1. A diagram illustrating some aspects of normal pituitary-adrenal function and the site of action of drugs which modify it. Physiological factors are illustrated by solid arrows, pharmacological ones by broken arrows. Inhibition or blockade is indicated by black boxes. *Physiological:* In the central nervous system a corticotrophin releasing factor (CRF) stimulates (I) the anterior pituitary to secrete corticotrophin (ACTH), which in turn causes (II) the secretion of the several adrenal hormones, only four of which are shown. Other humoral agents also influence (III) aldosterone secretion, but their identity is uncertain. Of the corticoids illustrated, hydrocortisone and aldosterone are the most important, the other two being produced normally in insignificant amounts. Hydrocortisone serves (IV) as the main natural inhibitor of ACTH secretion, thus providing a self-limiting regulatory system. It may act directly on the pituitary, the hypothalamus, or both (101). Exogenous stimuli (V) can, however, stimulate ACTH secretion, thus overriding the feedback mechanism (IV). Not illustrated is the possibility, for which some evidence exists, that the central nervous system exerts inhibitory as well as stimulating influences on ACTH secretion. *Pharmacological:* Depressant drugs (analgetics, tranquilizers, and so on) can inhibit (VI) the secretion of ACTH either by direct effects on the nervous system or by insulating it from exogenous sensory stimuli (V). Su-4885 acts (VII) primarily to inhibit the enzymatic hydroxylation of adrenal hormones at carbon-11, thus preventing or reducing the secretion of hydrocortisone and aldosterone. The lack of hydrocortisone eliminates the feedback mechanism (IV), permitting excess secretion of ACTH. Under these circumstances an excess of ACTH causes an outpouring of 11-deoxycorticosterone and 11-deoxyhydrocortisone. These are mineralocorticoids and their levels may rise sufficiently to cause sodium retention. If a steroid which inhibits ACTH (VIII) is given with Su-4885, all corticoid secretion is reduced and sodium diuresis and reduction of edema may occur. The spiro lactones act (IX) as competitive inhibitors of aldosterone and block its effects on the kidney and at other sites. This results in sodium diuresis and a compensatory hypersecretion of aldosterone. The DDD-like compounds cause (X) cellular atrophy of the adrenal, lack of responsiveness to ACTH, and decreased secretion probably of all corticoids.

sumably dependent upon a release of luteinizing hormone mediated by the central nervous system (7) as in the rabbit, by a variety of drugs (such as atropine, dibenamine, barbiturates, morphine, SKF-501, chlorpromazine, and reserpine) if they were administered at certain time-limited stages of the estrus cycle. Specifically this was between 2 and 4 P.M. on the day of proestrus (8, 9). Electrophysiological studies showed again that although several of these drugs seemed to have common actions in the central nervous system, no single common pattern of response was seen. This suggests strongly that the inhibition of ovulation achieved was effected at different sites. In the hen, ovulation can be blocked by drugs, but pharmacological details seem to differ from those seen in mammals: the barbiturates are inactive, but atropine and SKF-501 work (10). A drug used for the treatment of infectious diseases in birds [2-amino, 5-nitrothiazole (Enheptin)] causes dramatic gonad atrophy and sterility in chickens, apparently due to gonadotrophic inhibition (11). In mammals, however, this type of action is only transient if it is present at all (11, 12).

Studies with the newer tranquilizing drugs are of particular current interest. It is clear that reserpine, for instance, can affect anterior pituitary function in such a way as to inhibit estrus, menstruation, and fertility (13, 14) and modify the decidual response, which is dependent on the secretion of pituitary luteotrophins (15).

Interestingly enough, this inhibitory effect on certain gonadotrophins is not carried over to the lactogenic hormone of the pituitary, the release of which is certainly not inhibited by reserpine (13), but instead in some species (including man) and under some conditions is stimulated to the extent that lactation is induced. This was first seen in isolated clinical cases and was subsequently demonstrated unequivocally in animals (16, 17). A still different pattern of effects, discussed below, occurs in the release of ACTH, which may be either stimulated or depressed.

Syrosingopine, a compound derived by chemical modification from reserpine, is much weaker than the latter in influencing the release of gonadotrophins and lactogen (and ACTH) from the pituitary (17-19) and in causing tranquilization-sedation, although it is as effective as reserpine in reducing blood pressure in laboratory animals.

Unlike reserpine, it reduces catecholamine levels much more at peripheral than at central sites (20). Hence it may be inferred that the endocrine effects of *Rauwolfia* alkaloids are mediated primarily in the brain.

Chlorpromazine has, in general, endocrine effects much like those of reserpine, but minor differences suggest that different mechanisms of action are involved.

It is a curious fact that very scanty manifestations of such actions of reserpine and chlorpromazine have been obtained in the millions of patients treated with these drugs. One reason may be that the dosage required to obtain anything other than subtle evidence of activity is larger than dosages usually used in medical practice; such effects are more frequently seen in psychiatric practice, where large doses are conventionally used (21). This means that these drugs will probably never be effective therapeutic agents for the controlled and purposeful regulation of reproductive functions in man. These findings do, however, point clearly to the fact that such pharmacological regulation is possible. Drugs which act more specifically would be of great potential use, both in clinical medicine and in animal husbandry, in treating reproductive dysfunction and in controlling—particularly in inhibiting—fertility. In this connection the hoped-for application of the gonadotrophin-inhibiting effects of extracts of the *Lithospermum* plants, a heritage from the American Indian, have not yet been realized.

Despite their gonadotrophin-suppressing action, as seen in the rat (8), the use of barbiturates and other anesthetics as inhibitors of ovulation has not had, and probably will not achieve, practical application.

Recent reports show that different monoamine oxidase inhibitors, including the "psychic energizer" iproniazid, in relatively high dosage, can suppress gonad function and produce sterility in rats (22). It is probable but not certain that the major effect involves a selective inhibition of certain gonadotrophins, perhaps the interstitial cell-stimulating hormone.

In conclusion, it is of interest that all of the drugs mentioned above, believed to affect reproductive functions in mammals through modification of gonadotrophin secretion, are drugs which act on the autonomic or central nervous systems. Generally they act on some aspect of the metabolism of the neuro-

humoral catechol amines. Here similarity ends, however, because sites and details of their action vary widely. This emphasizes again the point that the chain of neurohumoral influences in the control of reproduction is a long one, with many points of pharmacologic vulnerability.

Gonad hormones. Studies have been continued over many years in an attempt to find steroids which, by competitive inhibition or otherwise, would antagonize the action of the natural hormonal steroids. With the exception of the recent work on antialdosterones discussed below, these efforts have been largely fruitless. The natural estrogens and androgens themselves may show either antagonistic or supplementary effects when given together, the result being dependent upon the end point chosen. A few nonhormonal steroids can interfere with the action of natural ones to a moderate degree (23, 24). Perhaps the recent finding of an anti-androgenic activity of A-norprogesterone represents the greatest success in this direction (24). In general, however, such work has not contributed greatly either to experimental or to clinical endocrinology.

The recent discovery of the antiestrogenic action of the new nonsteroidal compound, 1-(*p*-2-diethylaminoethoxyphenyl)-1-phenyl-2-*p*-methoxyphenyl ethanol (Mer-25), provides a tool of much greater potential importance. In rats, mice, monkeys, chicks, and rabbits, it will block the action of endogenous or exogenous estrogens, either steroidal or nonsteroidal, with remarkable effectiveness (25). The mechanisms of action are not known. In addition, in the rat it causes degeneration of fertilized eggs in the oviducts, even when given after mating, and thus prevents pregnancy (26). Whether this is a consequence of its antiestrogenic action or a separate effect is not certain (27). The potentials of a compound with these properties in the treatment of reproductive disorders and of tumors and in fertility control are great. The danger is, however, that such compounds, like the estrogenic doisylnic acid derivatives and some adrenal cortical inhibitors, tend to have a high degree of species specificity. They may work in man as in animals, but enthusiasm must be tempered until that is demonstrated to be the case. In fact, there is an ominous lack of reports of activity of Mer-25 in man.

One of the first effects of sex steroids

on the uterus seems to be the release of histamine (28), to which some later reactions are presumably secondary. Also, histamine is apparently involved in other hormone-triggered uterine events, such as the formation of deciduomata. Antihistamine drugs can, therefore, block some actions both of the estrogens and of progesterone in animals (28, 29). As yet there has been no practical application of this interesting fact. Ergotoxine can block estrus cycles, pseudo-pregnancy, and pregnancy in rats by means which are not clear (30).

A considerable variety of chemical compounds, such as the antimetabolic drugs, alkylating agents, and antimetabolites, can interfere with the activity of the germinal epithelium or other aspects of the reproductive process and produce sterility. Such work has been extensively reviewed by Jackson (31) and Nelson (4); it does not appear that endocrine mechanisms are primarily involved.

Drugs Affecting the Adrenal Cortex

Adrenocorticotrophin inhibitors. With the partial exception of aldosterone, the secretions of most of the hormones of the adrenal cortex are regulated by ACTH (Fig. 1). The mechanisms regulating the rate of secretion of ACTH itself, aside from the feedback system, are labile ones; they are highly sensitive to a wide variety of stimuli which can best be grouped under the term *stressful*. In general, the system seems designed to insure that an excess of adrenal corticoids will be available for any potential need. The frequency with which this system is deranged so that a harmful excess of corticoids is released is a moot point, but that this sometimes happens is certain.

It is probable that the varied stimuli, either enhancing or inhibiting, which affect ACTH secretion impinge in common on the central nervous system by either neural or vascular routes. It is generally believed that they are all funneled through the hypothalamus, but this is not certain (32). There, it is thought, they cause a release of corticotrophin-releasing factor, which follows vascular paths to the anterior pituitary and causes ACTH secretion. It is, therefore, not surprising that the most effective inhibition of ACTH release has been achieved by (i) surgery which blocks either neural paths to the hypothalamus

or vascular paths leading from it to the pituitary, or (ii) drugs which are depressants of the central nervous system. Of the latter, none has the advantage of specificity or of complete effectiveness. Nevertheless, some have served as useful laboratory tools; the term *chemical hypophysectomy* has entered the literature, although it probably suggests more than any drug has yet accomplished.

Among the drugs which can block or dampen the release of ACTH under some circumstances are the following: SKF-501 (33, 34), morphine (35-37), dibenzylamine (34, 36), atropine (34), barbiturates (38, 39), diphenylhydantoin (40), meprobamate (41), reserpine (42), ether (39), and chlorpromazine (43, 44). These are, for the most part, the same drugs which can inhibit secretion of certain gonadotrophins, suggesting common pathways of action. In general, they probably act either at central sites to prevent release of the corticotrophin-releasing factor or peripherally to prevent afferent stimuli from reaching such central sites. None of them prevent ACTH secretion completely—that is, they do not produce adrenal insufficiency, but rather tend to prevent the normal extra release of ACTH following stressful stimuli (45). Their primary end action is on the secretion of glucocorticoids rather than of aldosterone, since the latter is only partially under the control of ACTH. The groups led by Sawyer and by Sayers (39) agree in the suggestion, based on various types of neurological and pharmacological evidence, that several of these drugs, such as morphine, chlorpromazine, the barbiturates, and ether, act primarily to depress the reticular activating system and thus prevent stimuli that release the corticotrophin-releasing factor from reaching the hypothalamus. Royce and Sayers (39) provided the direct evidence of changing blood levels of ACTH (as contrasted to indirect measures of ACTH secretion) under the influence of ether and barbiturates.

Despite certain common end results, the drugs involved differ considerably among themselves with respect to details of their actions. It should be emphasized that the majority of them, when first administered, act like stressors and may cause an initial massive outpouring of ACTH. For this reason their ACTH-suppressing activity may easily be overlooked. In the case of reserpine the initial ACTH-releasing action can itself be blocked by dibenamine (46). Subsequently the stimulatory action subsides

and the drugs tend to block the ACTH-releasing effect of other stimuli. This has been notably demonstrated in studies on morphine and reserpine (35, 42, 47). The barbiturates, on the other hand, seem to depress ACTH release without a prior stimulation. The extent to which the drugs studied block the action of ACTH-releasing stimuli seems to vary with the drugs themselves, with their dosage, and perhaps with other experimental variables. Interestingly enough, Gold and his co-workers (48) found that chlorpromazine and some other tranquilizers, but not reserpine, will block the pituitary response to the adrenal inhibitor Metopirone (Su-4885), discussed below. Mepazine, a phenothiazine, has a predominantly stimulating action and little if any inhibitory action on ACTH secretion (49).

It is interesting to speculate on the practical and therapeutic consequences of this type of pharmacology. In psychic agitation, in shock or in pain, is the ACTH-inhibiting or ACTH-stimulating action of drugs conventionally prescribed one aspect of their therapeutic efficacy or an undesirable side effect? No certain answer can be given. Most of the substances involved protect against various forms of shock, but it is not known whether the adrenal-pituitary effects in such situations are coincidental or more directly related to the end results. In chronic stress a good theoretical argument could be made that a dampening of adrenal activity is advantageous. It is clear only that this long-overlooked aspect of the pharmacology of "depressant" drugs should be considered in an assessment of their total activity.

Whatever may be the medical aspects of the use of such drugs, they have acquired a highly practical laboratory role in that they dampen endogenous hypothalamic-pituitary activity and thus facilitate the study of other agents which affect the release of the corticotrophin-releasing factor and of ACTH (see, for example, 43, 50).

Direct inhibitors of the adrenal cortex. Now that some systematic effort to find them is being made, it seems that there are a variety of pharmacological ways, other than by inhibition of ACTH, in which corticoid suppression can be achieved. Such suppressants might be expected to be useful in hypertensive disease, cardiac and renal diseases, diabetes mellitus, neoplasms, and other states more definitely related to adrenal hyperfunction, such as Cush-

ing's syndrome, primary aldosteronism, and adrenogenitalism. In addition, some have proved useful diagnostic tools. Scientific attention at the moment is focused largely on three types of compounds which act on the adrenal in different ways. These are the steroidal spiro-lactones, the amphenone-like compounds, and compounds related to the insecticide 1, 1-dichloro-2, 2-bis (*P*-chlorophenyl) ethane (DDD). Of perhaps greater future promise is the existence of preliminary evidence that various other types of compounds may have similar activity.

Steroidal spiro-lactone (see Fig. 1). The original work of Kagawa *et al.* (51) and of Liddle (52), followed by that of many others, established that a group of steroidal lactones can act competitively to prevent aldosterone and other mineralocorticoids from having their typical sodium-retaining effects in the kidney and at other sites. This work has been well confirmed, and the therapeutic value of spiro-lactone as a diuretic and antihypertensive has been established (53). The gonadal steroids with previously known weak natriuretic effects act like the spiro-lactones (54). More important, perhaps, is the possibility that the discovery of the spiro-lactones will open the door to the discovery of other long-sought-for competitive inhibitors of adrenal and gonadal steroids. Much effort has already been expended in that direction without any notable success.

Inhibitors of steroidogenesis in the adrenal. The compound amphenone B was synthesized by Allen and Corwin (55) and then shown by Hertz *et al.* (56) to have a multiplicity of biological effects, among which was a suggested inhibition of adrenal cortical function in the rat. The other effects included progestational, antithyroid, and anesthetic actions, and in the rat a marked adrenal hypertrophy with cholesterol deposition.

It subsequently became clear that in the dog and in man amphenone interferes with the biosynthesis of all or most of the adrenal corticoids, probably by interfering with the enzymatic mechanisms responsible for the later stages of steroid synthesis (57). Rosenfeld and Bascom (58) located these inhibitions as specifically involving 11 β -, 17 α - and 21-hydroxylations as well as the oxidation of the 3-hydroxyl to 3-ketone. By manipulating the amphenone molecule it is possible to vary the potency and at least the quantitative pattern of its

activities (59, 60). One can, for instance, enhance or depress the antithyroid activity, and this in itself would be of practical interest were it not that other types of antithyroid drugs of much greater potency and specificity are available.

In our laboratory a large number of compounds more or less closely related to amphenone have been studied. One of particular interest (Fig. 1) was Metopirone (Su-4885). It was first noted in dogs (61) that in acute experiments this compound eliminated or reduced the Porter-Silber steroids in adrenal vein blood and blocked their production by adrenal tissue of rats and guinea pigs *in vitro* (59). It seemed curious at the time, however, that when given to dogs over a long period it did not cause adrenal insufficiency and, in fact, under some conditions caused a retention of sodium, suggesting an excess of mineralocorticoid. The explanation of this paradox turned out to be, as shown independently by Liddle *et al.* (62) and Jenkins *et al.* (63), whose findings were subsequently abundantly confirmed, that in ordinary tolerated doses in intact animals or man, Su-4885 inhibits primarily 11 β -hydroxylating mechanisms (Fig. 1) and hence inhibits secretion of the main natural corticoids—hydrocortisone, corticosterone, and aldosterone. If its action stopped at that point, the drug could have a wide potential usefulness in many disease states. The withdrawal of hydrocortisone from the circulation, however, removes the principal natural inhibitor of ACTH secretion. The consequent excess of ACTH acting on adrenals whose main pathways of steroidogenesis are blocked causes an outpouring of two steroids normally secreted only in very small amounts: 11-deoxyhydrocortisone (Reichstein's S) and 11-deoxycorticosterone. These are both potent salt-retaining hormones, and their presence adequately explains the observed salt retention and lack of adrenal insufficiency. The endocrine effects of Su-4885 duplicate closely those observed in a hypertensive syndrome described in man by Eberlein and Bongiovanni (64), due to a congenital incapacity to hydroxylate steroids at carbon-11.

These secondary actions of Su-4885 will probably preclude or limit its use in long-term therapy. The history of the drug, however, provides another example of the fact that the practical consequences of research may be totally unforeseen when the research plan is

formulated. Metopirone is finding a wide use as a tool in the differential diagnoses of pituitary-adrenal diseases. This is based on the fact that if the ACTH secretory mechanism is normal, a patient will respond to Su-4885 by excess secretion (and excretion) of 11-deoxy-steroids; the lack of such response shows a specific pituitary deficiency. In addition, if an ACTH inhibitor (for example, prednisone) is given with Su-4885, then the compensatory rise in 11-deoxy-mineralocorticoids is prevented and a sodium diuresis, useful in some conditions, is achieved (65).

Work now in progress in our own and other laboratories suggests that compounds with a different spectrum of effects than either amphenone or Su-4885 can be made. Such developments will be awaited with great interest.

DDD-like compounds (see Fig. 1). The insecticide DDD and related compounds have a different type of action in that they cause cytotoxic atrophy of the dog's adrenal, with a consequent reduction in steroid secretion (66). The adrenals of DDD-treated animals, unlike those of animals receiving the amphenones, are not responsive to ACTH as regards either growth or secretory activity. Apparently a considerable family of DDD-like substances have adrenal-inhibiting activity, and a search is being made for congeners with greater activity and less toxicity than the parent compound. None have been found that are both safe and effective for human use, but *o,p'*-DDD has rather dramatically inhibited the development of metastatic adrenal carcinoma as well as adrenal function in man (67).

Miscellaneous substances. Numerous other substances have been reported to cause some manifestations of adrenal inhibition. These include the strong antithyroid drug thiouracil, which causes some adrenal atrophy in rats (68); it is interesting to note that the adrenal inhibitor amphenone is also a thyroid inhibitor. The estrogens cause adrenal hypertrophy; this is an apparent compensatory response to their action in inhibiting a maximal corticoid synthesis, perhaps due to some interference with cholesterol metabolism (69). Another substance, delta-4-cholestenone, also interferes with the synthesis of cholesterol and may in that way exert its reputed inhibitory effect on corticoid secretion (70).

A number of recent reports suggest that a variety of substances may act as adrenal cortical suppressants: strepto-

mycin (71), heparin (72), omega-methylpantothenic acid (73), triazines (74), and acetyl strophanthidin (75). Schuler and Meier (76) proposed, on the basis of indirect evidence, that some thiosemicarbazones were adrenal inhibitors. Interestingly enough, these thiosemicarbazones also cause testicular dysfunction, particularly of the germinal epithelium. We have found in preliminary direct measurements that two of these thiosemicarbazones, Ba 9479 and Ba 11044, markedly depress adrenal function, as determined by measurements of the steroid content of adrenal vein blood.

In tissue culture an antimutagenic action of hydrocortisone on HeLa cells can be blocked by pilocarpine (77). It will be interesting to explore the significance of such results in terms of whole organisms.

Although substances of wide therapeutic applicability are not yet at hand, the present situation, with its many opportunities for well-guided further investigations, differs greatly from that of the recent past when the existence of any pharmacological inhibitor of the adrenal cortex was questionable.

Antithyroid Drugs

Since this article is primarily concerned with current and prospective lines of investigation, only brief reference will be made to antithyroid drugs. Endocrine pharmacology has achieved, however, its greatest successes in this field; the extensive available knowledge is now recorded in textbooks, and the use of these drugs is well established in medical practice.

Thyrotrophin. In contrast to the huge number of substances which inhibit thyroid activity by some local action, there are few which are known to achieve a similar result by inhibiting the release of pituitary thyrotrophin. Thyroid hormones inhibit the release of pituitary thyrotrophin, and this is one of the main features of physiological thyroid regulation. A direct action of iodide on the secretion of pituitary thyrotrophin has often been suggested but has not yet been demonstrated (78). Dinitrophenol may have some effect, possibly an indirect one (79). Ether may inhibit the release of pituitary thyrotrophin (80) as well as ACTH. Reserpine certainly has a mild thyroid-inhibiting action in some circumstances, which is thought to result from inhibi-

tion of the release of pituitary thyrotrophin (81).

Direct thyroid inhibitors. Thyroid inhibition can be accomplished in various ways (82). One is based on the still anomalous fact that iodine, although a constituent of the thyroid secretion and hence necessary for its synthesis, can under certain circumstances act as a thyroid inhibitor (see 83). Thiocyanate and various monovalent ions close to iodine in the Hofmeister series interfere with the mechanism by which the thyroid normally can collect and retain large quantities of iodide from the blood stream (84). As a result of the pioneer work of the MacKenzies (85) and of Astwood *et al.* (86), some sulfonamides and thioamides related to thiourea were shown to block thyroid hormone production, probably by blocking the iodination of tyrosine in the thyroid. From the thioamides the most useful therapeutic agents for controlling hyperthyroidism have evolved: 2-thiouracil, propylthiouracil, methimazole, iothiouracil, and so on.

Subsequently a variety of other compounds was shown to have some sort of thyroid-inhibiting influence. These include resorcinol (87), phenothiazines (88), phenylbutazone (89), amphenone (56, 90), 2-3-dimercaptopropanol (91), reserpine (92), and some substances of natural origin—for example *Brassica* plants (79). These compounds probably act in different ways. None has yet had practical application.

Stimulants and Inhibitors of the Neurohypophysis

The two known hormones of the mammalian posterior pituitary are, according to the species, either arginine- or lysine-vasopressin and oxytocin. They are now generally thought to be neurosecretions, perhaps synthesized in hypothalamic nuclei from which they traverse neurones to a discharge point from the posterior lobe. The main known function of vasopressin is to increase the permeability of nephron walls to water, thus facilitating reabsorption and inhibiting excretion of this substance.

Study of influences which either stimulate or depress the release of vasopressin has been greatly impeded by the lack of sufficiently reliable and sensitive methods of measuring this hormone in body fluids when it is present in small amounts. Generally, stimulation

of the release of vasopressin is inferred if the whole pattern of response to a drug or other influence resembles the response to exogenous vasopressin. Inhibition is inferred if the response is like that in diabetes insipidus, induced either by surgical means or by water diuresis.

A large number of drugs, particularly those that produce some manifestation of toxicity, inhibit water diuresis in short-term experiments. It is common to assume that this is due to the release of vasopressin. In our experience, however, with rats as test animals, most such drugs were found to cause a shut-down not only in the excretion of water but in that of sodium and potassium as well. Under the same conditions exogenous vasopressin causes, if anything, an increase in the excretion of sodium and potassium along with water anti-diuresis. Hence, such evidence provides no certain basis for implicating the neurohypophysis. It is of great interest but uncertain significance that in the absence of vasopressin the action of thiazide diuretics are reversed—that is, they cause anti-diuresis (93).

Diuretic drugs. A plethora of drugs, many in wide clinical use, cause water diuresis and have varying effects on the excretion of electrolytes. Ethanol is the only one of these that, on the basis of widely acceptable evidence, acts by inhibiting the secretion of vasopressin. The diuretic action of ethanol-containing beverages has been commonly observed through the ages. It was hard to convince the pharmacologists, however, that this was a specific effect of ethanol *per se*. Agreement that such was the case emerged from the work of Edkins and Murray (94), of Eggleton (95), of Strauss *et al.* (96), and particularly of van Dyke and Ames (97). The latter workers added the convincing demonstration that ethanol acted to inhibit the release of vasopressin. This interesting work has not led to therapeutic applications. While ethyl alcohol is widely self-administered, to greater or lesser advantage, for psychopharmacological purposes, it is seldom a cure for edema. In fact, the finding of Laragh *et al.* (98) that surgical ablation of the posterior pituitary did not prevent the formation of ascites in the dog suggests that any future discoveries of vasopressin inhibitors would not provide tools, as once we had hoped, for the treatment of diseases characterized by anasarca. In the laboratory, however, ethanol enjoys wide use as a tool for making animals suitable for the bioassay of vasopressin-like sub-

stances by blocking the release of endogenous vasopressin. A compound with similar activity but less toxicity would be still more useful.

Drugs Affecting the Isles of Langerhans

The medical problem of diseases of the pancreas is of such magnitude that any means of pharmacological control of, or substitution for, that organ assumes great importance. The search for substitutes for insulin that could be given orally rather than by injection has been a continuing one. Several types of compounds are known to have insulin-like action, and in recent years two groups of these have found notable success in medical use, the sulfonylureas and the biguanides. The literature has been thoroughly cited in recent reviews and symposia (99). The discovery of the antibacterial action of sulfonamide drugs carried in its wake, as has often-times been the case in the history of science, some spectacular advances in entirely different fields of medicine. For one, certain sulfonamides (acetazolamide, chlorothiazide, hydrochlorothiazide, and so on) were found to be highly effective diuretic and antihypertensive agents. For another, some of the sulfonylureas were found to have an insulin-like hypoglycemic action and to be useful in the treatment of diabetes mellitus. The principal compounds involved have been tolbutamide, carbutamide, and chlorpropamide — drugs whose activities differ only in details. The main action of these drugs is to stimulate the release of pancreatic insulin. Other actions, such as an augmentation of insulin effects or direct actions on organic metabolism, are probable but ill defined.

The hypoglycemic action of some guanidines has been known for many years. It was only recently, however, that one of these, phenylethylbiguanide, found wide clinical use. Although considerable factual information exists concerning its effects, a comprehensive understanding of its mode of action is lacking. Clearly, however, it acts differently from either insulin or the sulfonylamides.

Since pancreatic hyperfunction is much rarer than pancreatic deficiency, there has been less incentive to find insulin inhibitors than insulin stimulants or substitutes. Nevertheless, such drugs have an important if limited role, and therefore much enthusiasm greeted the

discovery that alloxan and some related substances, when properly administered, could selectively destroy the insulin-secreting (beta) cells of the pancreas in animals (100). It was hoped that, among other things, alloxan might afford a practical means of control of pancreatic tumors and their metastases. These hopes were not wholly realized, but laboratory work has been greatly facilitated by the ability to produce an experimental diabetes at will with the use of alloxan. Not only is it much easier to give alloxan than to do a surgical pancreatectomy, but the selective destruction of beta-cells by alloxan, unlike surgical procedures, leaves other nonendocrine parts of the pancreas functionally intact.

Conclusions

There are a few well-established cases in which pharmacological regulation of endocrine secretion can be brought about in a highly effective and practical fashion by drugs. Prototypes exist, however, of drugs which can do the same thing less effectively for most of the other major endocrine glands, with the exception of the parathyroids. These drugs are of a great variety of types and act in many different ways. This provides a wide front from which future advances can be made, in both theoretical and applied endocrinology. It can be expected, therefore, that an endocrine pharmacology will develop comparable to the pharmacology that applies to the nervous system and to other organ systems.

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Formation of Radiocarbon

However, in 1939, just before the war, Serge Korff of New York University and others discovered that the cosmic rays produce secondary neutrons in their initial collisions with the top of the atmosphere. The neutrons were found by sending counters, designed to be sensitive to neutrons, up to high altitudes, and they were found to have an intensity which corresponded to the generation of about two neutrons per second for each square centimeter of the earth's surface.

Whereas it was extremely difficult to predict the types of nuclei that might be produced by the billion-volt primary cosmic rays, the neutrons, being secondaries, were in the million-volt energy range and, therefore, subject to laboratory tests. So at this point the question was: What will million-electron-volt neutrons do if liberated in the air? The answer to this question was already available—in fact, Korff noted in one of the papers announcing the discovery of the neutrons that the principal way in which the neutrons would disappear would be by forming radiocarbon. The reaction involved is a simple one. Oxy-

Radiocarbon Dating

The method is of increasing use to the archeologist, the geologist, the meteorologist, and the oceanographer.

W. F. Libby

Radiocarbon dating had its origin in a study of the possible effects that cosmic rays might have on the earth and on the earth's atmosphere. We were interested in testing whether any of the various effects which might be predicted

could actually be found and used. Initially the problem seemed rather difficult, for ignorance of billion-electron-volt nuclear physics (cosmic-ray energies are in this range) was so abysmal at the time (and, incidentally, 14 years later is still so abysmal) that it was nearly impossible to predict with any certainty the effects of the collisions of the multi-billion-volt primary cosmic radiation with air.

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gen is essentially inert to neutrons, but nitrogen is quite reactive. Nitrogen-14, the abundant nitrogen isotope, reacts essentially quantitatively to form carbon-14 with the elimination of a proton. It also reacts about 1 percent of the time to produce tritium (radioactive hydrogen); this is another story, leading to a method of dating water and wine.

To return to radiocarbon dating, knowing that there are about two neutrons formed per square centimeter per second, each of which forms a carbon-14 atom, and assuming that the cosmic rays have been bombarding the atmosphere for a very long time in terms of the lifetime of carbon-14 (carbon-14 has a half-life of about 5600 years), we can see that a steady-state condition should have been established, in which the rate of formation of carbon-14 would be equal to the rate at which it disappears to reform nitrogen-14. This allows us to calculate quantitatively how much carbon-14 should exist on earth (see Fig. 1); and since the two atoms per second per square centimeter go into a mixing reservoir with about 8.5 grams of carbon per square centimeter, this gives an expected specific activity for living matter of 2.0/8.5 disintegrations per second per gram of carbon.

The mixing reservoir consists not only of living matter, which dilutes the radiocarbon, but of the dissolved carbonaceous material in the oceans, which can exchange carbon with the atmospheric carbon dioxide and thus dilute it. In fact, the ocean is the larger part of the diluting carbon reservoir (see Table 1). For each square centimeter of the earth's surface, there are about 7.25 grams of carbon dissolved in the ocean in the form of carbonate, bicarbonate, and carbonic acid, and the biosphere itself contains about 0.33 gram per square centimeter of surface. Adding all the elements of the reservoir, we get a total of 8.5 grams of diluting carbon per square centimeter, and the two carbon-14 atoms disintegrating every second should be contained in 8.5 grams of carbon. Thus, the specific activity of living carbon should be that number. We find this to be the actual value observed, to within about 10 percent (see Table 2). Of course, the times for mixing of all parts of the reservoir must be short as compared to the average lifetime of radiocarbon, 8000 years. The time for mixing of the oceans is the longest, about 1000 years on the average.

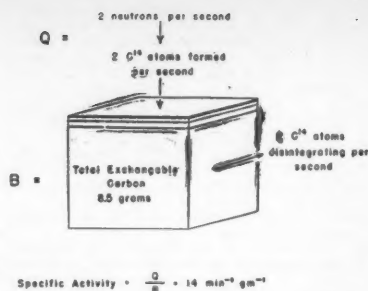


Fig. 1. Radiocarbon genesis and mixing.

This is interesting, for it means that the present intensity of the cosmic radiation (unless there have been canceling errors in our calculations) corresponds to the average intensity over the last 8000 years, the average life of carbon-14. It tells us, also, that the ocean is mixed nearly perfectly to its bottom depths in 8000 years. This we know because we included all of the dissolved carbon in the sea. Also, direct measurement of the carbonate and bicarbonate in deep ocean water confirms this. These conclusions could be false if errors in the very different quantities—the intensity of the cosmic rays and the mixing rate and depths of the oceans—should happen just to cancel one another. Since these factors are so unrelated, we believe this to be very unlikely and conclude that the agreement between the predicted and observed assays is encouraging evidence that the cosmic rays have indeed remained constant in intensity over many thousands of years and that the mixing time, volume, and composition of the oceans have not changed either.

We are in the radiocarbon-dating business as soon as this has been said, for it is clear from the set of assumptions that have been given that organic matter, while it is alive, is in equilibrium with the cosmic radiation—that is, all the radiocarbon atoms which disintegrate in our bodies are replaced

by the carbon-14 contained in the food we eat, so that while we are alive we are part of a great pool which contains the cosmic-ray-produced radiocarbon. The specific activity is maintained at the level of about 14 disintegrations per minute per gram by the mixing action of the biosphere and hydrosphere. We assimilate cosmic-ray-produced carbon-14 atoms at just the rate that the carbon-14 atoms in our bodies disappear to form nitrogen-14. At the time of death, however, the assimilation process stops abruptly. There is no longer any process by which the carbon-14 from the atmosphere can enter our bodies. Therefore, at the time of death the radioactive disintegration process takes over in an uncompensated manner and, according to the law of radioactive decay, after 5600 years the carbon that was in our bodies while we were alive will show half the specific carbon-14 radioactivity that it shows now. Since we have evidence that this has been true for tens of thousands of years, we should expect to find that a body 5600 years old would be half as radioactive as a currently living organism. This appears to be true. Measurements of old artifacts of historically known age have shown this to be so within the experimental errors of measurement.

Initial Research

The research on radiocarbon dating was carried out in several stages. In the first place, my collaborator, E. C. Anderson, and I had to determine whether the living material actually had the radioactivity expected. At that time we had no measurement techniques sufficiently sensitive to detect the radioactivities involved directly because these levels are quite low. Later we developed methods for making the measurement, but at that time we did not have them, so we used the method of concentrating the heavy isotope of carbon. An apparatus for this purpose had been built by and was being used by A. V. Grosse of Temple University, then of the Houdry Process Corporation at Marcus Hook, Pennsylvania. Grosse was concentrating the carbon-13 isotope for medical tracer purposes and kindly agreed to try to concentrate some biological methane for the test so crucial to our research. We had to use biological, as contrasted with petroleum, methane, for we had at this point ar-

Table 1. Make-up of the carbon reservoir (grams of carbon per square centimeter of surface) according to Anderson and Libby and W. W. Rubey.

	Anderson and Libby	Rubey
Ocean "carbonate"	7.25	6.95
Ocean, dissolved organic	0.59	0.78
Biosphere	0.33	
Humus	0.20	0.125
Atmosphere	0.12	
Total	8.5	7.9

rived at a distinction between living and dead organic chemicals. We had both "dead" methane and "living" methane in the sense that methane from oil wells in which the oil has been long buried would be expected to be entirely free from radiocarbon while the methane made from the disintegration of living organic matter should contain radiocarbon with an activity of 14 disintegrations per minute per gram of carbon. The task was to take this living methane and concentrate it in the isotope separation column to see whether the heavily enriched product was radioactive. Happily for our research, it was found to be so, and to about the expected degree. The material used was methane gas from the sewage disposal plant of the city of Baltimore.

The second stage of the research was the development of methods of measurement sufficiently sensitive to elimi-

nate the use of this \$10,000 thermal-diffusion isotope column, which was so expensive to operate that it cost thousands of dollars to measure the age of a single mummy. Obviously, radiocarbon dating would have been an impractical method of measuring archeological ages if this phase of the research had been unsuccessful.

Counting Technique

The counting method developed involves measuring the radioactivity of the carbon directly. We convert the samples by chemical methods into a suitable form—carbon dioxide or acetylene gas or even solid carbon—which then is placed inside a Geiger or proportional counter, where it itself constitutes the gas or lies on the inner counter wall. This is possible because carbon

as lampblack is an electrical conductor, and the gases carbon dioxide and acetylene are satisfactory counter gases. In this way a maximum count rate is achieved.

The counter itself is shielded from the background radiations in order to accentuate the carbon-14 count. A typical shield is shown in Fig. 2. It consists of 8 inches of iron to absorb the radiations from terrestrial sources, such as uranium, thorium, and potassium. The cosmic rays, however, which consist at sea level largely of μ -mesons, penetrate the thick iron shield readily, and whereas the count rate in the absence of the shield is about 500 counts per minute, the rate is decreased to about 100 counts per minute by the iron shield. This remaining activity, due in main part to μ -mesons, has to be removed. In order to do this, we surround the counter, with the carbon dating sample in it, with a complete layer of Geiger counters in tangential contact with one another and wire them so that when any one of these counters counts, the central counter with the dating sample is turned off for about one thousandth of a second. In this way the μ -mesons are eliminated from the record, so the background radiation comes down to something between 1 and 6 counts per minute, depending on the details of counter and shield design. This is for a counter of about 1 liter volume, capable of holding up to 5 grams of carbon with counting rates of 75 counts per minute for living carbon, 37.5 counts for 5600-year-old carbon, and 18.7 and 0.7 count, respectively, for 11,200-year-old and 56,000-year-old carbon.

After we had developed a technique for measuring natural carbon relatively inexpensively with the requisite accuracy, our next job was to determine whether the following assumption was sound: that the variation of radiocarbon production due to the variation of the cosmic rays with latitude (which is very strong indeed) would be wiped out by the movement of the winds and the ocean currents in the 8000-year lifetime of carbon-14. The plan was to measure living materials from various places on earth and to see whether they had the same radiocarbon content per gram of carbon. These data on the natural abundance of radiocarbon in the earth were presented by E. C. Anderson for his doctoral thesis at the University of Chicago. They showed no appreciable differences, even though the samples came from places varying in latitude

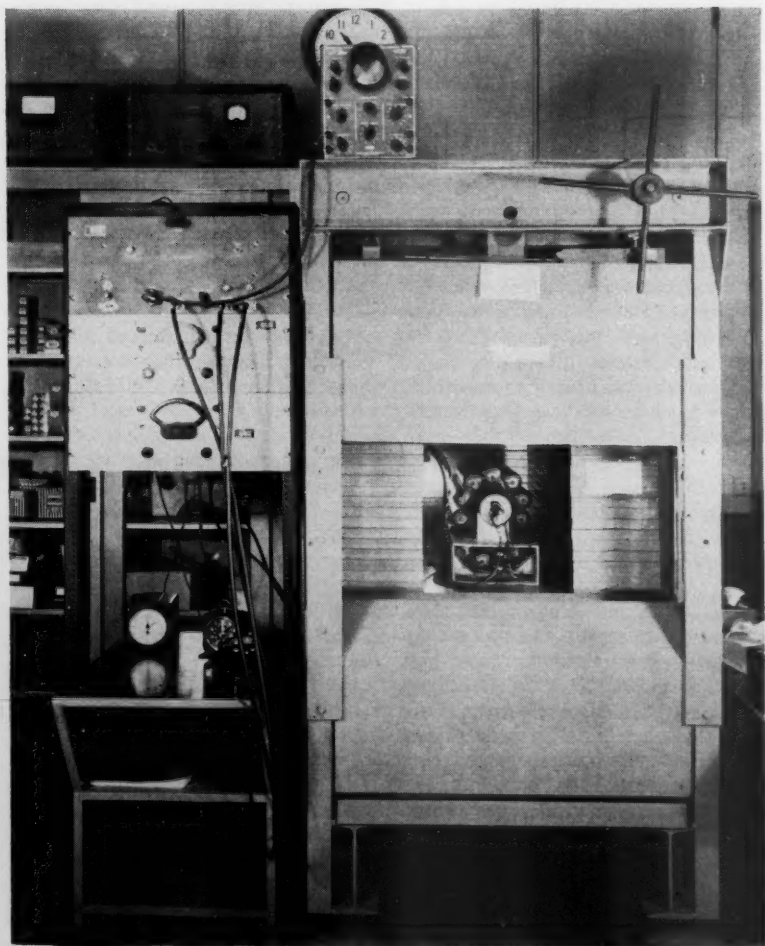


Fig. 2. Radiocarbon counting apparatus.



Fig. 3. (Above) Human hair, 5020 ± 290 years old, of an Egyptian woman. (Right) Preglacial wood, more than 20,000 years old, from a glacial moraine in Ohio.

from near the South Pole to near the North Pole (Table 2) (1). At the present time, 10 years later, no evidence for variation has been found except in areas of extensive carbonate deposits where the surface waters may carry a considerable amount of old carbon dissolved, and thus reduce the carbon-14 level below the world-wide average for the biosphere-atmosphere-ocean pool as a whole. Fortunately, such conditions are relatively rare and generally easily recognized.

Dating Technique

After the study of the natural occurrence of radiocarbon, the next stage was to see whether we had a method of dating artifacts of a known age, a problem which led us to mummies. J. R. Arnold joined us at this stage. We had a decay curve drawn which predicted, with no unknown factors and no adjustable constants, the specific activity of ancient organic matter. And so the question was to see whether it worked. The first thing we had to do, of course, was to get the materials for measurement. This was done by enlisting the cooperation of the American Anthropological Association and the Geological Society of America. Geologists have been quite interested in the results of this dating technique from the beginning, even though its reach in time is short for many of their problems. A committee of advisers, consisting of Donald Collier, Richard Foster Flint, Frederick Johnson, and Froelich Rainey, was appointed to select the samples for us and to help us collect them. These gentlemen worked hard

for several years, assisting and collecting the samples and advising us.

The research in the development of the dating technique consisted of two stages—dating of samples from the historical and the prehistorical epochs, respectively. Arnold and I had our first shock when our advisers informed us that history extended back only for 5000 years. We had thought initially that we would be able to get samples all along the curve, back to 30,000 years before the present; we would put the points in, and then our work would be finished. You read statements to the effect that such and such a society or archeological site is 20,000 years old. We learned rather abruptly that these numbers, these ancient ages, are not known accurately; in fact, the earliest historical date that has been established

with any real certainty is about the time of the 1st Dynasty in Egypt. So we had, in the initial stages, the opportunity to check against samples of known age, principally Egyptian artifacts, and in the second stage we had to go into the great wilderness of prehistory to see whether there were elements of internal consistency which would lead one to believe that the method was sound or not.

For the prehistoric period, members of our committee set up a network of problems which were designed to check, in as many ways as possible, points of internal consistency. They set out about a dozen major projects, and we collected samples (see Fig. 3) from each of these projects and worked hard and measured them; similar measurements are still going on now, 10 years later.

Table 2. Activity (in disintegrations per minute per gram) of samples from the terrestrial biosphere.

Source	Geomagnetic latitude	Absolute specific activity
White spruce, Yukon	60°N	14.84 ± 0.30
Norwegian spruce, Sweden	55°N	15.37 ± 0.54
Elm wood, Chicago	53°N	14.72 ± 0.54
<i>Fraxinus excelsior</i> , Switzerland	49°N	15.16 ± 0.30
Honeysuckle leaves, Oak Ridge, Tenn.	47°N	14.60 ± 0.30
Pine twigs and needles (12,000-ft alt.), Mount Wheeler, N.M.	44°N	15.82 ± 0.47
North African briar	40°N	14.47 ± 0.44
Oak, Sherafut, Palestine	34°N	15.19 ± 0.40
Unidentified wood, Teheran, Iran	28°N	15.57 ± 0.31
<i>Fraxinus mandshurica</i> , Japan	26°N	14.84 ± 0.30
Unidentified wood, Panama	20°N	15.94 ± 0.51
<i>Chlorophora excelsa</i> , Liberia	11°N	15.08 ± 0.34
<i>Sterculia excelsa</i> , Copacabana, Bolivia (9000-ft alt.)	1°N	15.47 ± 0.50
Ironwood, Majuro, Marshall Islands	0°	14.53 ± 0.60
Unidentified wood, Ceylon	2°S	15.29 ± 0.67
Beech wood, Tierra del Fuego	45°S	15.37 ± 0.49
<i>Eucalyptus</i> , New South Wales, Australia	45°S	16.31 ± 0.43
Seal oil from seal meat from Antarctica	65°S	15.69 ± 0.30
Average		15.3 ± 0.1

Curve for Samples of Known Age

Figure 4 shows the curve of "knowns"—the results obtained for samples of known age as compared to the carbon-14 decay curve drawn with the value of 14 disintegrations per minute (the value for living matter) taken as unity and with a half-life of 5568 ± 30 years. The half-life itself was measured in 1949 in collaboration with A. G. Engelkemeir, W. H. Hamill, and M. G. Inghram and found to be 5580 ± 45 years, a value which, when combined with independent values of 5589 ± 75 obtained by W. M. Jones and 5513 ± 165 obtained by W. W. Miller, R. Ballentine, W. Bernstein, L. Friedman, A. O. Nier, and R. D. Evans, gave 5568 ± 30 by weighting according to the inverse square of the errors quoted. Remeasurements are now being made, by Mann at the National Bureau of Standards in Washington and by Olsson at the University of Uppsala.

The knowns are in two main groups—those measured by us at the University of Chicago and those measured by Miss Ralph at the University of Pennsylvania, labeled (C) and (P), respectively. One sample, "Pompei," was measured by E. A. Olson and W. S. Broecker of the Lamont Geological Observatory.

The oldest samples of known age measured were "Hemaka" and "Zet" from the 1st Dynasty in Egypt. Both were wood found in the subterranean brick structures of the 1st Dynasty tombs of the Vizier Hemaka and of King Zet, both at Saqqara. Hemaka was contemporaneous with King Udimu, and both tombs were generally agreed to date from 4900 ± 200 years before the present. The next oldest samples were cedar wood from the upper chamber of the Southern Pyramid of Sneferu at Dahshur. The next sample, marked "Sesostris," is a very interesting one. It is a part of the deck of the funeral ship which was placed in the tomb of Sesostris III of Egypt and is now in the Chicago Museum of Natural History. It is about 20 feet long and six feet wide and is quite an imposing object, complete with paddles. The next sample is "Aha-nakht." It consists of wood, probably cedar, from the outer sarcophagus of Aha-nakht, at El Bersheh. It was found in the tomb, which was covered with earth. The coffin was presumably excavated by the natives at the same time as the El Bersheh coffin obtained for the British Museum by E. A. W. Budge, after 1895.

As we proceed up the curve, the next

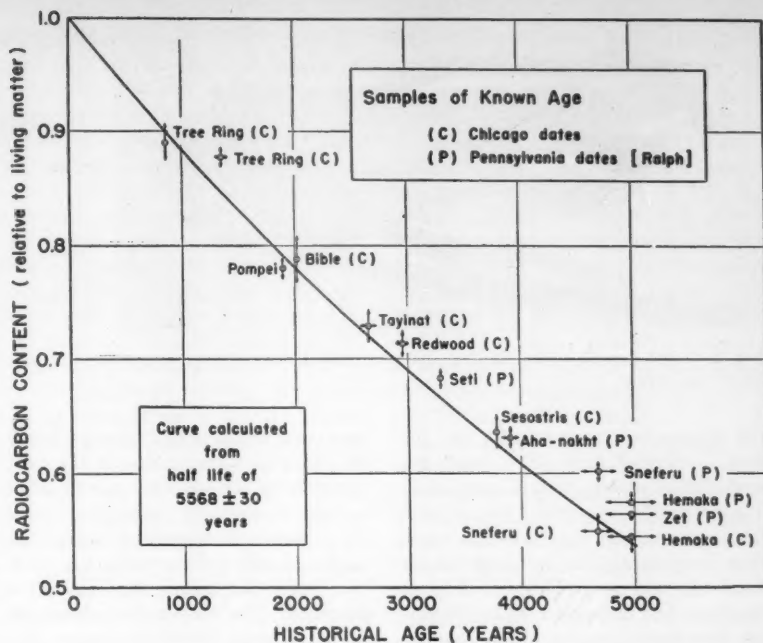


Fig. 4. Curve of knowns.

sample is the heartwood of one of the largest redwood trees ever cut. The tree was known as the "Centennial Stump," felled in 1874. There were 2905 rings between the innermost (and 2802 rings between the outermost) portion of the sample and the outside of the tree. Therefore, the known mean age, determined according to the tree-ring method of Douglas, was 2928 ± 51 years, as of the time it was cut. This is an interesting point, as it shows that, in the heartwood of the *Sequoia gigantea* at least, the sap is not in chemical equilibrium with the cellulose and other large molecules of the tree. In other words, the carbon in the central wood was deposited there about 3000 years ago, although the tree itself was cut just a few years ago. The next sample, which is marked "Tayinat," is from a house in Asia Minor which was burned in 675 B.C. It was wood from the floor of a central room in a large *hilani* ("palace") of the "Syro-Hittite" period in the city of Tayinat in northwest Persia. Its known age is 2625 ± 50 years.

The next sample is the linen wrapping of one of the Dead Sea scrolls, the Book of Isaiah, which was found in Palestine a few years ago (Fig. 5). The next sample, labeled "Pompei," was carbonized bread from a house of ancient Pompeii; still looking like an overdone roll, it was charred by the volcanic ashes that buried the city in

79 A.D., roughly 1880 years ago. The other samples are wood, dated by the Douglas tree-ring-counting technique. When results from these samples are taken all together, the agreement with the predicted radiocarbon content seems to be satisfactory. The errors are given as the counting errors (standard deviations) only.

It is certainly possible that the decay curve, which is drawn on the basis of a half-life of 5568 years, could be drawn somewhat differently. However, it is well to know that all radiocarbon dates published today have been calculated on this half-life, and in order to avoid confusion we should be careful about changing the basis of the calculation of radiocarbon ages before the evidence for a change in half-life is definite. The curve of knowns seems to indicate that a slightly longer half-life might be permissible. However, there are other possible explanations of a deviation of the curve of knowns from the theoretical curve. We all await the results of the half-life researches of Mann and Olsson with great interest.

Perturbations

It has been observed that fossil carbon dioxide from the combustion of coal and oil, after about 1870, began to dilute the biosphere and to reduce



Fig. 5. (Left) Peruvian rope, 2632 ± 200 years old. (Right) Linen wrapping, 1917 ± 200 years old, of the Book of Isaiah, one of the Dead Sea scrolls.

the radiocarbon content, and that the trend continued until 1954, when the explosion of atomic devices reversed it. The carbon-14 introduced by the neutrons produced in the explosions more than compensated for the reduction by the fossil carbon—a reduction which at that time had amounted, in the Northern Hemisphere, to about 3 percent of the primeval level as far back as it has been possible to measure it, from tree rings. H. L. de Vries and Hans E. Suess have been particularly active in research on this point. It was Suess, in fact, who discovered that fossil carbon dioxide had been reducing this specific activity in recent biospheric material, since 1870.

Broecker and Olson have made careful studies of the carbon-14 content of ancient woods as well. And the general result is that there appear to have been, prior to 1870, only very minor variations, of the order of 1 percent or less, in the radiocarbon content of living matter. The recent perturbations are of no great concern for archeologists and geologists now living. Of course, in the future it will be difficult to correct for the period when these perturbations were active; that is, 5000 years from now there may be some difficulty in understanding why, for a period of a century or so, beginning in 1870, the radiocarbon level was so perturbed. However, the written records may well explain the anomaly; in fact, radiocarbon dating as such may not be needed to establish historical fact.

Dating the Last Ice Sheet

After the curve of knowns had been drawn, the next step in the research was to test in the great periods of prehistory to see whether the dates obtained were reasonable. Perhaps the

most interesting single general result for this prehistoric period is the time in which the last ice sheet moved down to cover the northern part of the United States and the European continent. The result, $11,400 \pm 200$ years, has now been well established by the radiocarbon technique. The radiocarbon dates for this cataclysmic development show that it happened simultaneously in Europe and in North America and that the phenomenon was very widespread, and that it had a tremendous impact on the living habits of people the world over. The oldest sign of man in northern Europe and in England is younger than this, presumably because of the thoroughness with which the glacier removed all sorts of human artifacts. Therefore, the oldest of the Scandinavian, the English, and the North American occupation sites are all about 10,400 years old, dating back, presumably, to the time when the ice sheet receded.

In Fig. 6 are plotted, for the Americas, the number of occupation sites versus age. It is quite clear that there is an abrupt discontinuity at about 10,400 years. In Europe, however, if instead of examining sites in the northern regions we look at sites in the Mediterranean basin, there is no discontinuity, and evidences of human occupation extend back as far as the radiocarbon dating technique can reach—50,000 years or so. There seems to be some contrast between this and the situation in the Americas, where, as shown in Fig. 6, one sees a decided difference in the total number of sites in preglacial times. In view of the fact that it is known that extensive areas of the Americas were not glaciated by the last ice sheet, this raises something of a question. There is, of course, the definite possibility that this is pure accident, and it even seems possible that we do

now have human sites in the Americas which are definitely older than 10,400 years. However, the weight of the evidence seems to indicate that something in the nature of a discontinuity occurred at that time. Most of the sites that are older than 10,400 years are equivocal in one way or another, at least so it seems to the chemist or physicist who overhears the archeologists arguing about them. We have noticed that there is considerable unanimity of opinion about American sites of 10,400 years or younger being human sites, whereas, there is considerable discussion and debate concerning the older sites. This is not true in Southern Europe and Asia Minor. One of the most remarkable of the sites in Europe is the Lascaux Cave in Central France, which has the beautiful paintings on the walls, showing the ancient animals in such authentic style as to demonstrate the remarkable advancement of the culture of the people at that time. These paintings are presumably older than 15,000 years, the age determined for the charcoal found in the soil of the cave. Around Asia Minor and in the areas of the Middle East there is no scarcity of materials which date back as far as radiocarbon dating can reach, and there is considerable evidence that the sites are human sites.

In Geology, Oceanography, and Meteorology

In addition to its use in the work on human history, radiocarbon dating has been used for geological purposes to a considerable extent. Of course, the time span of radiocarbon is so short, as compared to the history of the earth, that most geological problems are outside the reach of the technique. But

recent history and recent events do fall within its scope, and there have been a number of investigations, in particular the sorting out and measuring of the chronological events of the recent ice ages—that is, the relative times of arrival of the various ice advances and the periods of time between them, the points of simultaneity, and the identification of particular moraines with particular advances. On these points, small and perhaps relatively unimportant as they are, the geologists have found radiocarbon dating to be of some use.

In oceanography, the great question of the rate of mixing of the oceans has yielded to the radiocarbon technique to a considerable extent, particularly in the hands of Suess and of Broecker and Olson—Suess particularly in the Pacific and Olson and Broecker in the Atlantic. They have shown that the Pacific mixes relatively less rapidly, the turnover time being something between 1500 and 2000 years, whereas the Atlantic mixes relatively more rapidly, at a rate about twice this, or with a 750- to 1000-year turnover time. It is clear from these researches that the fundamental assumption of radiocarbon dating, that the reservoir of the sea must be counted as a diluent for the cosmic-ray carbon-14, is valid. Further, it has been shown by Suess that there will be opportunities of measuring the deep ocean currents. He finds evidence for velocities and directions of the deep ocean currents in the Pacific corresponding to a requirement of some hundreds of years for the passage northward along the bottom.

In meteorology, radiocarbon dating has been of some use. It has been interesting to observe the changes in the radiocarbon content in living matter near large industrial centers where the rate of production of carbon dioxide from coal and oil was highest, and also to observe the dissemination of the radioactive carbon made by atomic explosions in the atmosphere. From these things we know that world-wide mixing occurs. We observe the effects of changes generated very largely in the Northern Hemisphere quite clearly in the Southern Hemisphere, though they are reduced somewhat in intensity. This is the first time that there has been clear and incontrovertible evidence for such a world-wide circulation, and on a time scale of a very few years; such evidence is particularly clear in the case of the bomb-test carbon-14.

In Archeology

Of course, the main use of radiocarbon dating is in archeology and the investigation of the history of man through the use of chemistry, for most ancient men did not write, and we have no written records except in Egypt, in Asia Minor, and in limited areas of Central America. Yet it is perfectly clear that 10,000 and more years ago people lived in a way that indicates they rivaled modern man in intelligence and capabilities. We have just to look at their handiwork to see this. The paintings in the Lascaux Cave, the handiwork of the ancient Indians in North America—particularly the basketry and the very skillfully made arrowheads (Fig. 7)—attest to their great capabilities. Where they came from perhaps we do not know, but we do know that they were very intelligent and very capable people.

Last spring, on Santa Rosa Island off the coast of California, friends of mine found a 6-foot skeleton, 10,400 years old, to judge by the radiocarbon measurements of Broecker of Lamont Geological Observatory on some charcoal found next to the skeleton. This is the same 10,400-year date which we have observed so often and which now marks the early evidence of man in Santa Rosa Island; the Lindenmeier site in Colorado; the Clovis site; the Lamus Cave in eastern Nevada on the Utah-Nevada border, continuously occupied

from the time of the melting of the last glacier 10,400 years ago down to the time when modern man came into the area; the Fort Rock Cave in Oregon, where the most beautiful basketry of ancient man was discovered—grass rope woven into sandals (Fig. 8, left) of beautiful shape and design, 300 pairs of them neatly stacked just as though in a community shoe store 9000 years old; and several other sites in the Americas. We see in this the evidences that man has been a long time learning to *write* history but has been *making* history for many thousands and perhaps tens of thousands of years.

In Central Europe the element of simultaneity, which is revealed by the radiocarbon dates for the people who did not write or leave records, establishes conflicts and clashes between cultures which are interesting to examine and speculate upon. The Neanderthal man and the Cro-Magnon man did not stay long together. The Neanderthal man disappeared, and the Cro-Magnon man won; he may have been the man who painted the beautiful Lascaux Cave paintings, as I understand it from the archeologists.

We learn various details about the ancient peoples. For example, in the time of Hammurabi, the Babylonian king, there was an accurate calendar, but we have been uncertain about the correlation of this calendar with our own. This calendar of the Babylonians was a very good one, but there is an

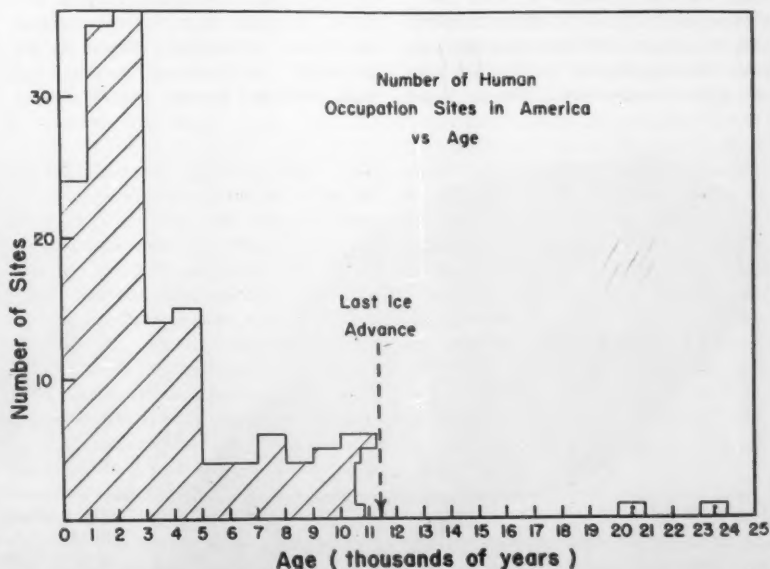


Fig. 6. Number of human sites in the Americas plotted against age.



uncertainty which, as I understand it, concerns the identification of a particular eclipse as we calculate it backwards in time in order to arrive at a correlation with our own calendar. Therefore, careful measurements were made on a portion of a house about 4000 years old that was precisely dated by the Babylonian calendar. In this case, a serious attempt was made to test the limit of sensitivity of the radiocarbon dating method. The sample of wood came from a beam from the roof of this house in Nippur, which bore a clear and legible date according to the Hammurabian calendar. The beam was divided into three equal portions; these were carefully measured (the total measurement time was three months), and the results for the three portions were then coordinated to obtain a definite answer as to which of the two most

likely correlations of the Christian and Babylonian calendars was correct. We concluded that the younger of the two possible calendars was strongly favored and that the odds against the other being correct were something like 9 to 1.

With the advancement of the radiocarbon dating technique and the consequent increase in accuracy, at least of the relative dates, it is possible to do more of these difficult jobs of pinpointing past events in time so as to drive back history into prehistoric periods and to more clearly delineate what really did happen in the development of man. Determination of the chronology of ancient civilizations may be said to be the main archeological problem and task of radiocarbon dating. As the technique is developed further and more fully and is more widely used, it

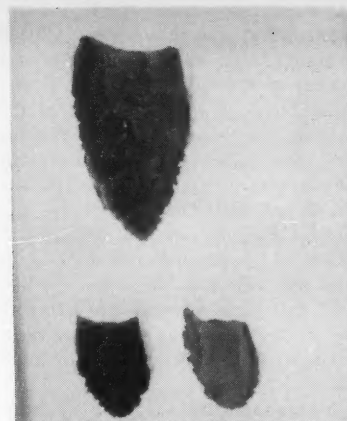


Fig. 7. (Left) Rush matting 3000 ± 250 years old, from a Nevada cave. (Above) Replicas of North American arrowheads from 10,000-year-old sites.

should be possible to excavate and utilize sites which are now hardly more than dark spots in some remote area. Charcoal is one of the best materials for radiocarbon dating, provided adequate care is taken to see that intrusive rootlets and humic acids are removed before measurements are made.

We intend, at the University of California, Los Angeles, to attempt to make a portable radiocarbon dater which will allow us to work in the field with the archeologists and geologists and thus to obtain dates which, though not as accurate as those which would be obtained in the laboratory, may be useful enough to serve as guides during the digging. The problem is to find a truck that will carry the rather heavy equipment over rough country. If this effort is successful, it will be a development which will bring the carbon daters

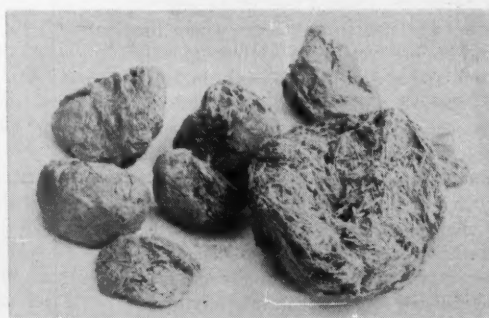
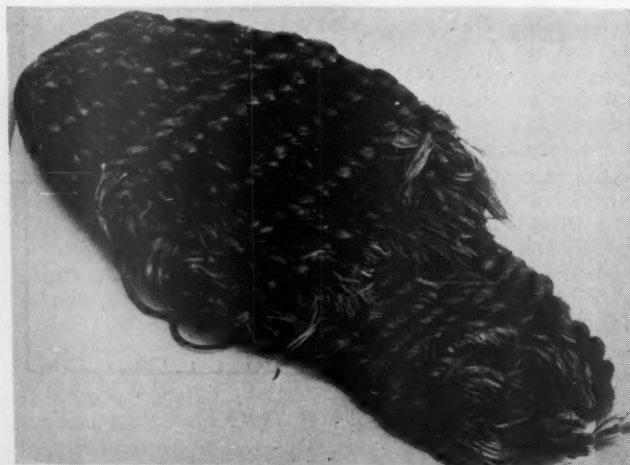


Fig. 8. (Left) Rope sandal found in eastern Oregon cave 9035 ± 325 years old. (Above) Dung of an extinct ground sloth, $10,455 \pm 340$ years old.

and the archeologists and geologists even closer together. Of all the rewards of research, none is greater than that of meeting people in different fields and finding interests in common. It will be most refreshing and rewarding for the radiocarbon daters to go out and share, at least vicariously, in the great thrill of an archeological dig.

Accuracy of the Results

The many people who have contributed to the development of the radiocarbon dating technique (several of whom I have mentioned but many of whom I have been unable to mention) are largely responsible for whatever success it has had. We now have several thousand radiocarbon dates throughout the fields of archeology, geology, meteorology, oceanography, and other areas. From examination of the results it is possible to form an opinion as to the general reliability and general weaknesses of the method. I am sure that Arnold would agree with me in saying

that it has lived up to our fondest hopes.

It was clear from the beginning that there would be difficulties about the samples. Anyone knows that it is possible to get dirt into solid matter which is lying in the ground, even if it is there only for a brief period, let alone many thousands or tens of thousands of years. The saving aspect of the situation, however, is that it is very much more difficult to mix molecules in such a way that they cannot be separated chemically, particularly in the case of substances such as charcoal and wood and cloth, and even, in certain instances, limestone and shale. One can separate and distinguish the contaminant from the original material and in this way disclose the real radiocarbon content. The researches of a number of people have validated the assumption that it is possible and that, indeed, it is not too difficult to obtain authentic samples in the field. In general, the samples may have to be inspected with some care under a relatively high-powered glass and then, possibly, treated with properly

chosen chemicals. But all of these things can be done, with techniques that are no more difficult than those used by the average hospital technician, and a sample can be obtained which should give authentic radiocarbon dates. The dating technique itself is one which requires care, but which can be carried out by adequately trained personnel who are sufficiently serious about it. It is something like the discipline of surgery—cleanliness, care, seriousness, and practice. With these it is possible to obtain radiocarbon dates which are consistent and which may indeed help roll back the pages of history and reveal to mankind something more about his ancestors and thus, perhaps, about his future.

Note

1. Our whole research was supported generously by the Viking Fund of New York City (now the Axel Wenner-Gren Foundation), the U.S. Air Force, the Geological Society, the Guggenheim Foundation, and, of course, the University of Chicago, where most of it was done.

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Science in the News

Kennedy on Natural Resources: His Program Covers Same Ground as Ike's, but on a Larger Scale

The Kennedy message on natural resources placed heavy emphasis on the role of the scientific community. The message proposed comparatively little spending for the coming fiscal year (1962), beginning this July. A spokesman for the Administration said he considered an extra \$100 million above Eisenhower's recommendations a reasonable guess. If Congress is cooperative, spending will surely be higher than this. But spending, in any case, will involve fairly small sums by the standard of the federal budget, and small also compared with what the program implies Kennedy would like to do in the years to follow.

Most of the recommendations for the coming year have to do with organizing a national attack on the problem of resources. Kennedy asked the National Academy of Sciences for a "thorough and broadly based study and evaluation of the present state of research." He said he wanted the Academy's recommendation for research programs affecting the "conservation, development, and use of natural resources, how they are formed, replenished, and may be substituted for, and giving particular attention to needs for basic research and to projects that will provide a better basis for natural resources planning and policy formulation." This study will take about a year and will cost about \$1 million. Its full impact will not show up until the fiscal '64 budget, which must be pre-

sented to Congress in January '63. Meanwhile, Kennedy asked the Federal Council for Science and Technology to recommend what can be done more quickly "to strengthen the total government research effort relating to natural resources."

The message included the by now familiar emphasis on oceanography. (The Democratic platform and the State of the Union message also included specific references to this, a continuation of an effort begun under the Eisenhower Administration to draw attention to the field.) The problem has been that the science, or the group of sciences collectively known as oceanography, has had difficulty winning Congressional support partly because it lacks the glamor and the obvious connection with national security that space and atomic energy research have, partly because responsibility for the program is scattered throughout the dozen or so government agencies with an interest in one phase or another of oceanography.

Presentation to Congress

One result has been that there is no single Congressional committee in either house with the authority to ap-

appropriate money for the whole program, and few of the committees have much interest in an area which is often apart from the major role of the agency asking for the money.

The most talked of example of this is the problem the Weather Bureau, which is part of the Department of Commerce, has had in getting even a comparatively small amount of money to do research on the effects of the ocean on the weather. The appropriations subcommittee with responsibility for the Department of Commerce has comparatively little interest to begin with in the Weather Bureau, and none at all in proposals of the Weather Bureau to do research in the oceans. When the committee begins looking for ways to cut the budget it is not surprising that it immediately questions the necessity of the Commerce Department supplying the Weather Bureau with several hundred thousand dollars to do research in the oceans.

A report on the problem appeared in *Science* (27 May 1960) and at the time there was talk of working out an arrangement for a single government office to present the whole program. Kennedy's natural resource message said something like this would be done, although it is not clear whether the effort can really be effective without changes in the law.

Fragmented Program

What the administration has in mind is to prepare a booklet bringing together all the pieces of the oceanography program now scattered through the budget, in the hope that this will make the appropriations subcommittees aware of the full range of the program. The Federal Council on Science and Technology, an arm of the President's office, would press the individual agencies to support their share of the program, a necessity since one of the problems has been that although oceanography has to come to enjoy high national priority, the segments of the program within individual agencies may have a very low priority in the agency programs. The work of the Federal Council would be a continuation of an effort begun under Eisenhower.

Finally, the Administration would present the program to the full Appropriations Committee. The presentation to the full committee, like the pamphlet, would be aimed at giving members of the subcommittees responsible for parts of the program a

picture of the program as a whole.

If such methods turn out to be effective they will probably be adopted for other programs, such as meteorology, which also are fragmented among a number of federal agencies. But a really effective solution of the problem may require changes in budget procedures, permitting a single agency to present the whole program to a single appropriations subcommittee, and then to assign funds for the parts of the program to the various departments.

Opposition to Reform

It would be hard to push such a reform through Congress, for any rearrangement of power over appropriations necessarily takes a little power away from some subcommittees and gives it to others. This makes it difficult to work out a reorganization, and the difficulty is compounded by the usually correct assumption that the drive behind the executive's pressure for reorganization is to make it easier for the Administration to get what it wants from Congress. This means that the relative power of the legislative branch is reduced and not only runs into Congress' disinclination to part with its prerogatives, but more importantly, arouses the opposition of conservatives in and out of Congress who, again usually correctly, feel that anything that makes Congress more efficient simply means more federal spending and a further expansion of federal powers.

In the face of such difficulties the Administration apparently does not intend to try for major reforms in budget procedures this year, when it already has its hands full trying to push through such things as the aid-to-education program. It is likely, though, that the attempt will be made during Kennedy's term. It would require a major effort by the President to arouse popular demand for reform, probably on the grounds that since present methods are inefficient, reforms would therefore save a great deal of money.

Resources Message

In general, the message on natural resources drew less public attention than any of the earlier ones: it contained neither a proposal so hotly debated as the aid for teachers' salaries of the education message or the medical insurance for the aged of the health message, nor did it deal, as did the messages on the economy and the gold

situation, with a problem that has been regularly making headlines. The message, in fact, was designed no more to present a program to deal with a problem than to draw the public and Congress' attention to the fact that a problem exists.

"Our entire society," the message said, "... is dependent upon our water, our land, our forests, and our minerals. How we use these resources influences our health, security, economy, and well being. . . . If we fail to use these blessings prudently, we will be in trouble within a short time. In the resource field, predictions of future use have been consistently understated. But even under conservative projections, we face a future of critical shortages and handicaps. By the year 2,000, a United States population of 300 million—nearly doubled in 40 years—will need far greater supplies of farm products, timber, water, minerals, fuels, energy, and opportunities for outdoor recreation. Present projections tell us that our water use will double in the next 20 years; that we are harvesting our supply of high-grade timber more rapidly than the development of new growth; that too much of our fertile topsoil is being washed away; that our minerals are being exhausted at increasing rates; and that the Nation's remaining undeveloped areas of great natural beauty are being rapidly preempted for other uses."

The message offered several dozen proposals covering these problems, and Administration spokesmen said that draft legislation would be soon sent to Congress. But the general purpose was to "bring together in one message the widely scattered resource policies of the federal government." On a larger scale, its purpose was essentially the same as the proposal to present a unified program on oceanography: to make Congress and the public aware of the need for a coherent national policy to deal with all the interrelated areas dealing with resources, and so to lessen the chance of the parts of the program being lost amidst the sea of often conflicting or overlapping legislation Congress must deal with each session.

Environmental Health

A substantial share of the message was devoted to the problems of air and water pollution, which it said had already reached alarming proportions. The nation is spending \$350 million a year on municipal waste treatment

works, a substantial sounding sum of money, but Kennedy said that nearly twice as much, \$600 million a year, is necessary just to keep pace with the growing rate of pollution.

The message charged that industry is "lagging far behind" in its treatment of wastes. It asked, as did the Eisenhower budget message, for stronger federal powers to deal with "serious pollution situations of national significance." It said air pollution is not only a growing health menace but that it causes an estimated \$7.5 billion a year damage to vegetation, livestock, metals, and other materials, and although a great deal of this lies beyond any control measures now feasible or even imagined, Kennedy recommended a major research effort to see what can be done to lessen the damage. He proposed a special unit to be organized by the Public Health Service to devote itself to the problem of air and water pollution, and recommended increases in the levels of federal grants to city and state governments for pollution control projects.

The Eisenhower budget message in-

cluded proposals, although on a smaller scale, along much the same lines. The idea of presenting a unified oceanography program to Congress, a proposal an Administration spokesman pointed to when asked what there was in Kennedy's message that was really new, grows out of an effort begun by the old Administration. Nearly all of the problems Kennedy described in his special message were touched on in Eisenhower's final budget.

How then, the spokesman was asked at a background briefing for the press, did the Administration see its policies as compared to Eisenhower's. "The previous Administration," he said, "recognized problems, but then only did enough to be able to say they were doing something; this Administration is really addressing itself to the problem." The Eisenhower view was that his Administration was indeed addressing the problem but at the same time was preserving a "sound balance" in the role of the federal government by restricting the programs to what seemed "necessary rather than merely desirable."—H.M.

News Notes

"The Dark Fence": Radar Screen Detects Orbiting Objects

The Navy has announced that the so-called "dark fence" will be completed later this year. It has been in partial operation for some months.

The screen will be created by a 500,000-watt transmitter (three smaller transmitters are now in operation) emitting a broad, thin radio curtain across the continent from southern California to Georgia. Reflections of objects in near space are picked up by gigantic receiver arrays, such as that illustrated. Data are fed into computers, and the orbits can be calculated. The system makes it possible to detect and track nonradiating satellites passing over this country. Navy officials said that even in its present partially completed form the system has detected and tracked a piece of wire 15 feet long orbiting at a height of 400 miles. The wire was debris from U.S. satellite.



Receiving antenna of the "dark fence" satellite detecting system, near San Diego, Calif. [U.S. Navy]

News Briefs

Polish-English translation. One of the objections which has been raised to cover-to-cover translation of scientific periodicals has been the time lag between the issuance of the original and the appearance of the translation. A first attempt to accomplish simultaneous publication of an original and its translation has now become possible under a Polish-English translation program administered by the National Science Foundation.

Beginning with the January 1961 issue (vol. 8, No. 1), an English edition of each issue of *Acta Biochimica Polonica* will appear at the time that the issue in Polish is available. The English edition will be prepared and printed in Poland and will be distributed free to those libraries which now receive translations from the National Library of Medicine under the PL 480 program.

* * *

Teen-agers. Teen-agers are bigger than they used to be. Insurance figures show that among boys 15 to 16 years of age there has been an average increase of 1.8 inches in height and 10 pounds in weight over a period of some 40 years; for boys of 17 to 19 the gain was 1.6 inches and about 10 pounds. Among girls of 15 to 16 the gain in average height was 0.6 inch and the gain in weight only a little over 1¼ pounds, while at 17 to 19 the girls gained, on an average, only 0.4 of an inch in height and actually showed a weight decrease of about 3 pounds. The Metropolitan Life Insurance Company reports that these facts are derived from a comparison of insured teen-agers in the Build and Blood Pressure Study, 1959, conducted by the Society of Actuaries, with teen-agers in an earlier study.

* * *

Nutrition: Army retirement credit. Army reserve officers who register for, and attend, certain sessions of the 25th meeting of the American Institute of Nutrition, to be held in Atlantic City, N.J., 10-15 April, will receive retirement point credits for such attendance. For further information, communicate with Lt. Col. Ernest M. Parrott, who will be at the Hotel Ambassador during the meetings.

* * *

Psychology journals. Elias Publications (P.O. Box 662, Washington 4, D.C.) has announced that the journal *Engineering and Industrial Psychology*

will be published as two quarterly journals, beginning in 1962. *Engineering Psychology* will contain original investigations on the adaptation of human tasks and working environment to the psychological and physiological attributes of human beings. *Industrial Psychology* will publish studies reporting the results of the application of psychological principles and methodology to problems in personnel management. Submission of manuscripts is invited by both publications.

* * *

East German publications. The American Mathematical Society and the East German publishing house Deutsche Verlag der Wissenschaften have entered into an agreement under which scientific publications of the latter will be made readily available in this country. These include works on mathematics, physics, chemistry, biology, economy, geography, geology, meteorology, and philosophy, and 12 scientific journals.

Under the new arrangement, the AMS headquarters offices will process orders and undertake the billing and collection of amounts due the Deutsche Verlag der Wissenschaften. Delivery of publications will be made directly to the purchaser or subscriber via airmail from Leipzig, at list price plus cost of packing and shipping. Members of the AMS will be given a reduced rate. Deutsche Verlag der Wissenschaften catalogs may be obtained from the American Mathematical Society, 190 Hope St., Providence 6, R.I.

* * *

Medical genetics. A short course in medical genetics (heredity and disease in man and animals) will be held for the second time in Bar Harbor, Me., 6-18 August. The course, which is supported by the National Science Foundation, is conducted through the collaboration of members of the faculty of the Johns Hopkins University and the staff of the Roscoe B. Jackson Memorial Laboratory.

The course is intended primarily for members of the faculty of medical schools; however, a few representatives from other areas will be accepted. Applications from recent medical school graduates interested in medical genetics will also be considered. Enrollment will be limited to 45. There is no registration fee. Application should be made to: Dr. Victor A. McKusick, The Johns Hopkins Hospital, Baltimore 5, Md.

Grants, Fellowships, and Awards

Algae. The Committee on the Darbar Prize of the Botanical Society of America will accept nominations from both members and nonmembers for an award to be announced at this year's meeting of the society in Lafayette, Ind. Under the terms of the award bequest, approximately \$250 will be given for meritorious work in the study of the algae.

The committee will base its judgment primarily on papers published in English by the nominee during the two calendar years previous to the closing date for nominations. At present, the award will be limited to residents of North America. Nominations, accompanied by a statement of the merits of the case and by reprints of the publications supporting the candidacy, should be received *before 1 June* by the chairman of the committee, Robert W. Krauss, Botany Department, University of Maryland, College Park, Md.

Marine biology. A postdoctoral fellowship program is being established in the Marine Laboratory of the University of Miami with the aid of a grant from the National Heart Institute. Objectives of the program will be to afford opportunities for those trained in other biological disciplines to acquire experience with marine organisms. Fellowships will be tenable for 1 year; stipends will be in the neighborhood of \$5000, with suitable dependency allowance. Further details and application blanks may be obtained from Dr. Charles E. Lane, Program Director, The Marine Laboratory, 1 Rickenbacker Causeway, Miami 49, Fla.

Mathematics. The Mathematics Research Center of the United States Army at the University of Wisconsin, Madison, offers graduate fellowships in mathematics for 1961-62 to afford opportunity for study directed chiefly toward the fields of applied mathematics and the related fields of mathematical analysis. A candidate must be a U.S. citizen and have a bachelor's degree in mathematics, physics, or engineering, and he must obtain admission to the Graduate School of the University of Wisconsin. The proposed course of study must be approved by the director of the Mathematics Research Center.

A fellowship holder is expected to devote his full time to study that leads to a master's or doctor's degree. The fellowships pay tuition and university fees and provide annual basic stipends

of either \$2250 or \$2500, depending on whether or not the recipient holds a master's degree. These stipends are increased by \$500 for fellows with children. A fellow may not engage in other regular remunerative employment or receive other concurrent fellowship aid.

Mycology. The Gertrude S. Burlingham scholarship in mycology for advanced predoctoral study at the New York Botanical Garden will be available for the summer of 1961. The stipend is \$700. Work under this appointment may begin at any time after 1 June and should continue for approximately 3 months. Nominations or applications should be sent *before 15 April* to the Director, The New York Botanical Garden, New York 58, N.Y.

Nutritional science. Applications for traineeships in experimental nutritional science at Philadelphia General Hospital are now being accepted, according to Henry W. Kolbe, executive director. Trainees selected will work under Paul Gyorgy, director of the PGH department of pediatrics, who was recently awarded a 4½-year grant of \$274,806 by the National Institutes of Health.

Applicants, either men or women, must have a doctorate in medicine or a related scientific field. Stipends of from \$3000 to \$8000 will be paid, depending upon the qualifications and academic position of the trainees. For information write to Dr. Paul Gyorgy, Department of Pediatrics, Philadelphia General Hospital, 34th and Curie Avenues, Philadelphia, Pa.

Psychoanalysis. The Association for Group Psychoanalysis, Inc., is offering a limited number of scholarships for its basic course in group psychoanalysis, to be provided for the seventh season in 1961-1962. For further information, write to the association at Apt. 4B, 50 E. 72nd St., New York 21, N.Y.

Radiological physics. A 1-year course in radiological physics, leading to the degree of master of science, is offered under the auspices of the department of radiology of the College of Physicians and Surgeons of Columbia University. The course is designed to prepare candidates to carry out all the functions of a physicist in a hospital department of radiology; it would also provide a foundation for those who wish to engage in research or applications in radiologic physics, radiation protection, and dosimetry.

As part of its national program for the training of radiological health spe-

cialists, the Division of Radiological Health of the U.S. Public Health Service has awarded a grant to the university that will provide financial assistance to qualified candidates. This aid will be in the form of tuition waivers, as well as monthly stipend allowances. Applicants must be citizens of the United States or must have filed a Declaration of Intent. Preference will be given to candidates who are sponsored by public health agencies for work in their area of responsibility or in closely related fields. Inquiries should be addressed to Dr. H. H. Rossi, 630 W. 168th St., New York 32, N.Y.

New Journals

Journal of The Forensic Science Society, vol. 1, No. 1, Sept. 1960. S. S. Kind, Ed. Forensic Science Society, c/o Rossett Holt, Pannal Ash Road, Harrogate, Yorkshire, England. Semiannual (September and March). £2 per year.

Journal of Chemical Documentation. 1961. H. Skolnik, Ed. American Chemical Society, 1155 16th St. NW, Washington 6, D.C. Semiannual. Nonmembers, \$10 per year; members, \$7.

Nuclear Fusion, vol. 1, No. 1, Sept. 1960. J. G. Beckerley, Ed. International Atomic Energy Agency, Kärntner Ring 11, Vienna, Austria. Quarterly. S. 250 per year.

Botanical Bulletin of Academia Sinica, vol. 1, No. 1, June 1960. H. W. Li, director. Institute of Botany, Academia Sinica, Nankang, Taipei, Taiwan. Irregular, \$2 per volume (one or two issues).

Pure and Applied Chemistry, vol. 1, No. 1, Sept. 1960. Official Journal of the International Union of Pure and Applied Chemistry. B. C. L. Weedon, Ed. Butterworth Inc., 7235 Wisconsin Ave. NW, Washington 14, D.C. Irregular. \$18 per volume (four issues).

Journal of Theoretical Biology, vol. 1, No. 1, Feb. 1961. J. F. Danielli, Ed. Academic Press, 111 5th Ave., New York 3, N.Y. \$17 per year.

Journal of Atherosclerosis Research and Scientific Reports of the Istituto Superiore di Sanità, 1961. Elsevier Publishing Company, Spuistraat 110-112, Amsterdam, Holland.

Polymer Science U.S.S.R., Sept. 1960. G. M. Burnett, trans. Pergamon Institute, 122 E. 55th St., New York 22, N.Y. \$60 per year. Single issue, \$15.

Studdi si Cercetari de Biochimie, No. 1, 1960. E. Macovschi, Ed. Academiei

Republicii Populare Romine, str. Popovici nr. 20, Bucharest, Romania. 5 lei.

Physics and Chemistry of Glasses, vol. 1, No. 1, Feb. 1960, and *Glass Technology*, vol. 1, No. 1, Feb. 1960. R. W. Douglas, Ed. Society of Glass Technology, Thornton, Hallam Gate Road, Sheffield 10, England. Bimonthly. Each £6 15s a year; joint annual subscription, £10.

Scientists in the News

Pierre Dansereau, dean of the science faculty and director of the Botanical Institute of the University of Montreal, has been appointed assistant director of the New York Botanical Garden, effective 1 April.

Dansereau has done extensive work in botany in Quebec Province, in several western states of the United States, and in South America and Europe. He will go to New Zealand in April for several months' research and lecturing before taking over his new duties.

Judson Hardy, public affairs officer of the Division of Radiological Health, Public Health Service, has been appointed chief of the public information section in the Office of Research Information, National Institutes of Health. He assumed his new duties on 27 February. He succeeds **Clifford F. Johnson**, recently named chief of the Office of Research Information.

Frank W. Newell, professor and chairman of ophthalmology at the University of Chicago, has been named a founding member from the United States on the international Problem Commission in Neuro-ophthalmology. The first meeting of the newly formed commission will be held 18 and 19 March in Geneva.

Nathaniel Arbiter, professor of mineral engineering at Columbia University, received the 1961 Robert H. Richards award of the American Institute of Mining, Metallurgical and Petroleum Engineers on 1 March for his contributions to the mineral industries.

Arnoldo Gabaldón, malariologist and Venezuela's Minister of Health and Welfare, and Sir **Gordon Covell** of the United Kingdom have been named co-recipients of the seventh Darling Foundation medal and prize for their work on malaria. The award, which was pre-

sented during the 15th World Health Assembly, held in New Delhi in February, honors the memory of Samuel Taylor Darling, malariologist who died in the service of the Malaria Commission of the League of Nations.

Gabaldón was director of, and later consultant to, the Division of Malariology at Maracay, Venezuela, for several years. He organized international courses in the study of malaria and insect-borne diseases.

Covell, author of numerous works on malaria, was director of the Malaria Institute of India from 1936 until 1947. He has also been adviser on malaria to the British Ministry of Health and director of the Malaria Reference Laboratory at Horton Hospital, Epsom, Surrey.

Theos J. Thompson, professor of nuclear engineering at Massachusetts Institute of Technology, director of the M.I.T. Reactor Project, and a member of the Atomic Energy Commission's Advisory Committee on Reactor Safeguards since 1959, has been named chairman of the committee for a 1-year term. He succeeds **Leslie Silverman**, professor of engineering in environmental hygiene at Harvard University School of Public Health, who served as chairman during 1960.

Choh-Yi Ang, director of materials laboratories for P. R. Mallory and Company, Indianapolis, has been appointed manager of Telecomputing Corporation's physics research laboratory in San Diego.

Richard A. Colgan, Jr., general manager of the Shasta Forests Company, Redding, Calif., was recently elected president of the Forest Genetics Research Foundation at Berkeley. Colgan was formerly associated with Diamond Match Company and the National Lumber Manufacturers Association.

The State University of New York Downstate Medical Center, Brooklyn, has announced the appointment of two visiting faculty members for March 1961. **Sir Dugald Baird**, Regius professor of midwifery and gynecology at the University of Aberdeen, will be visiting professor of obstetrics and gynecology, and **Margery Grace Ord**, fellow at Lady Margaret Hall College and member of the university demonstrator's department of biochemistry at Oxford University, will be visiting senior lecturer in pathology.

Max M. Marsh, head of Eli Lilly and Company's analytical research department since 1956, has been named a control associate. Marsh has established several methods for automatic analysis of amino acids, cholesterol, and other materials and was instrumental in developing a method for determining diethylstilbestrol in pharmaceuticals.

Richard S. Morse, former director of Army Research and Development, has been appointed Assistant Secretary of the Army (Research and Development). The newly created position includes responsibility for Research and Development Tests and Evaluations procurement and budget monitoring. Heretofore these responsibilities have been divided among several agencies, each responsible to the Secretary of the Army.

Before he joined the Department of the Army, in June 1959, Morse was president of the National Research Corporation, Cambridge, Mass., which he organized in 1940.

The Bureau of Commercial Fisheries, Fish and Wildlife Service, has presented two fishery biologists with citations for meritorious publications.

Winner of the top award was **Elbert H. Ahlstrom**, director of the Bureau's Biological Laboratory at La Jolla, Calif., for his work on the vertical distribution of fish eggs and larvae in the California current system.

The second award went to **Fred Berry**, who was staff biologist at the Bureau's Biological Laboratory at Brunswick, Ga., when selected. He is now with the La Jolla Laboratory. Berry's work was an extensive study of the jack family, an important group of forage and predatory fishes.

Robert B. Howell, Lockheed Missiles and Space Division engineer, was honored at the Institute of Aerospace Sciences' annual meeting in New York for "outstanding scientific contributions in the art of advanced theoretical guidance and control, and development of digital trajectory programs." He received the Lawrence Sperry Award and was cited for his work on the Polaris missile, for which Lockheed is prime contractor.

Jay L. Lush, professor in the department of animal husbandry at Iowa State University, received the Hermann von Nathusius Medal from the Deutsche Gesellschaft für Züchtungskunde last fall in Hannover, Germany.

John Buck of the National Institutes of Health is the new president of the Society of General Physiologists.

Sheldon Cholst, practicing psychiatrist formerly associated with New York University's School of Medicine and with the Institute of Physical Medicine and Rehabilitation at the university's medical center, has been chosen as producer, writer, and narrator of *International Science and Technology Review*, a weekly radio program. The program, which summarizes outstanding scientific events in 12 nations, is distributed by the Broadcasting Foundation of America, the international division of the National Educational Television and Radio Center.

Recent Deaths

Andrew W. Contratto, Brookline, Mass.; 54; associate director and chief of medicine of the Harvard University Health Services and senior associate in medicine at Peter Bent Brigham Hospital, Boston; 21 Feb.

Emile Henriot, professor emeritus of physics at the Université Libre de Bruxelles; prior to his retirement, was director of the physics department of the Faculté des Sciences; known for the creation of the rapidly rotating tops from which the Beams ultracentrifuge was developed; Feb.

Albert G. Hogan, Columbia, Mo.; 76; professor emeritus of animal nutrition at the University of Missouri; held academic posts at Kansas State University and Alabama Medical School; made numerous contributions to the field of nutrition; his studies led to the recognition of folic acid as a vitamin and the development of an assay for it; 25 Jan.

Howard R. Lillie, Brussels, Belgium; 58; president of the International Commission on Glass and staff research manager in the research and development division of Corning Glass Works; recognized for his research on glass viscosity; 15 Feb.

William D. Reeve, New York, N.Y.; 77; retired professor of mathematics and former head of the department of mathematics at Teachers College, Columbia University; author or coauthor of 16 textbooks on mathematics teaching; Feb.

Thomas O. Walton, Bryan, Tex.; 77; president of Texas Agricultural and Mechanical College from 1925 to 1943; 18 Feb.

Book Reviews

On Thermonuclear War. Herman Kahn.
Princeton University Press, Princeton, N.J., 1960. xx + 651 pp. \$10.

According to Herman Kahn, if deterrence is to be used to advance or maintain our position in a world of power politics, we must have the will to use the weapons if deterrence fails—that is, we must accept the position that thermonuclear war would not be annihilating, at least not over the next decade or so, and that, with careful planning, recovery from a nuclear attack is possible in a few years. Kahn argues that we must have the weapons needed to meet a variety of possible situations, ranging through bluffs, blackmail, and accidents to irrational behavior. That is, we must be able to (i) deter an attack by creating the fear of retaliation from a damaged Strategic Air Command or the fear of a preemptive strike by SAC following a tactical warning; (ii) deter provocative action by creating the fear of a premeditated first strike at the nation offering provocation; and (iii) deter provocative action by having the capability for counteraction which is expected to be so effective that the net effect of the "aggressor's" action would be a loss in his position. Necessary components of this posture include civil defense, a capability for limited war, a preattack mobilization base, and, hopefully, arms control.

The bulk of the book is devoted to by far the most detailed and lucid analysis yet presented of the kinds of weapons systems, mobilization bases, and postattack planning and resources required to meet situations which might involve military power. Even so, as Kahn is at pains to demonstrate, much more study is necessary before an evaluation can be made of the full implications of his position on such problems as the long-term biogenetic effects of radiation resulting from large attacks, the feasibility of blackmail techniques, the flexibility of the war plans in retaliation missions, and command and con-

trol. But the fundamental utility of his analysis rests on whether his thesis is valid: Kahn argues that thermonuclear war will not be annihilating (of social systems, if not all men) and, therefore, that if we are faced with "intolerable" or "outrageous" provocations we ought to be prepared to accept the social and material costs of recovering from a thermonuclear war rather than the costs of avoiding that war.

"Recovery" to near-normal prewar levels (as contrasted to politically, socially, and technologically primitive ways of life) depends crucially on the effective fulfillment of "seven optimistic assumptions: 1) favorable political environment, 2) immediate survival and patch-up, 3) maintenance of economic momentum, 4) specific bottlenecks alleviated, 5) 'bourgeois' virtues survive, 6) workable post-war standards adopted, and 7) neglected effects unimportant." However, in estimating the validity of these assumptions, Kahn does not apply the same careful analysis he used on hardware to the human condition in the postattack period. The considerable data available from history and the laboratory about the behavior of groups, individuals, and leaders under extreme threat, in the face of sudden disaster, or in ambiguous situations is ignored. Also ignored are the profound problems of establishing adequate, integrated leadership and command and control in a postattack society, for such a society may well be bereft of many layers of responsible, trained, civilian leaders. Nor does he discuss adequately the enormous problems of managing nationwide evacuations (historical examples are not analogous here), operating large fallout shelters during many days of occupancy, and training shelter-management cadres as well as insuring their presence in the shelters.

As a result of these oversights Kahn's statements about the behavior, values, and aspirations which could be expected to prevail under these disaster conditions are inadequate, incorrect, and glib to the extent that doubt is cast on

the plausibility of his optimistic assumptions. It is also well worth noting that there is nothing in his analysis which gives reason to believe that recovery could be accomplished under democratic forms of government.

As to peacetime planning for post-attack recovery, much could be done to accomplish the things necessary for recovery if sufficient research, planning, and implementation has been carried out, but it is very likely that this could be accomplished *only* through imposed or voluntarily accepted approximations of a garrison state. It seems clear, on the basis of several studies, that the required degree of peacetime integration and control of economic, political, institutional, and personal activities would very likely conflict with traditional concepts of the private and public rights and privileges of Americans.

Thus, Kahn's book is profoundly useful in four ways: (i) It should force any one who proposes to say anything about deterrence to stop talking vagaries and shibboleths. (ii) It should force those espousing Kahn-type weapons systems to recognize the crucial need for the same detailed study and analysis of people and leadership under ambiguous threat as that already given to thermonuclear hardware and tactics. (iii) Since Kahn's military approach is idealistic (it demands unstinting national commitment to logical behavior under all conditions), the book should make acceptable the study of other idealistic political or social approaches to the crisis. (iv) Since democratic values might well be lost in preparing for or in recovery from nuclear attack (and since the chances of their eventual revival are moot), the book should force a searching inquiry into the choice of means in preserving ends in a world of crises and political change everywhere.

DONALD N. MICHAEL

*Brookings Institution,
Washington, D.C.*

Talent and Education. E. Paul Torrance. University of Minnesota Press, Minneapolis, 1960. x + 210 pp. \$4.50.

One of the 16 authors quotes Norbert Wiener's statement: "Let those who choose to carve a human soul . . . be sure that they have a worthy image after which to carve it, and let them know that power of molding an emerg-

ing intellect is a power of death as well as a power of life." Those who are engaged in the business of educating talented young persons are carving human souls; sometimes with skill, sometimes not; sometimes with substantial knowledge of what they are doing, sometimes without. For such persons, this volume, which consists of the papers presented at the 1958 Institute on Exceptional Children held by the University of Minnesota, provides a useful summary of information on the nature of human abilities, some of the psychometric approaches to the study of talent, crucial factors in the life histories of talented persons and in the development of scientists, some of the means by which schools attempt to give special treatment to exceptionally able students, and the treatment of individual differences in Russian schools. Also included are brief reports of several exploratory studies concerning bright students and their school and postschool careers.

The book is mostly synthesis and review with relatively little new information. An exception is Catherine Cox Miles' study of the life histories of 100 prominent Americans who died during the period 1936-1940 and the comparison of their early life histories with those of 300 geniuses who constituted the subjects of her earlier study. Choosing among the papers is partly a matter of personal interest. I liked best John E. Anderson's good review of the nature of human ability and Anne Roe's brief summary of studies that she and R. D. McCurdy conducted on the school and home influences that make a scientist.

DAEL WOLFLE

*American Association for the
Advancement of Science*

Oxford Regional Economic Atlas of the Middle East and North Africa. Economist Intelligence Unit. Oxford University Press, New York, 1960. viii + 56 pp. + 64 maps and gazetteer (15 pp.). Cloth, \$10; paper, \$5.25.

This atlas, the second of what promises to be an extremely useful series (intended eventually to cover the world), touches on many facets of the physical and economic-social phenomena characterizing the Middle East and North Africa. C. G. Smith of Oxford University served as geographical adviser, and the volume was prepared by the Econo-

mist Intelligence Unit (a research group of the British periodical *The Economist*) and the cartographic department of the Clarendon Press.

The scale of the maps varies; about half of the sheets presented are on a common base map of the entire area and are shown at a scale of 1:19 million (300 miles to the inch). The detailed regional sheets are shown on scales ranging from 1:10 million (176 miles to the inch) for the Sudan, Ethiopia, and Iran to 1:6 million (95 miles to the inch) and 1:4.25 million (67 miles to the inch) for the other countries. The maps lack a graphic scale with distances actually drawn on the map and the reader must carry his own ruler if he is to determine distances. The regional maps are easily read. The elevation tints are unobtrusive and consist of warm shades of greens and browns with soft gradation from one to another. There is coverage of the geology which gives the geological period—Cretaceous, Jurassic, and so forth—of the surface rocks with short notes about the characteristic relief developed in each case. The treatment is as detailed as the scale of 1:19 million will allow. Relief is shown at the same scale. Here a plastic relief effect is achieved by the now common device of imposing mountain or hill shadows on the elevation tints. This gives a gross indication of the relief and is useful as a heuristic technique, but there is a serious objection. The map gives an impression of roundness to some extremely jagged landscapes. I cite the arid zone scarp of the north side of the Qattāra depression in Egypt, the walls of the great rift as it bisects Ethiopia, and the rough moon-like landscapes of the Hadramout and Yemen coasts of southern Arabia. Relief can be symbolized more realistically, though less colorfully, by the black-and-white diagrammatic technique developed by Irwin Raisz.

The soil and vegetation maps are generally well handled, though the categories used in describing the vegetation of the more tropical areas are not sufficiently specific. The sheets covering rainfall and water balance are the most sophisticated I have seen in a general atlas. Annual rainfall is shown, as well as rainfall temperature diagrams for 19 representative stations. The diagrams show the usual average monthly progression of rainfall and temperature against a background of the actual rainfall received each month for the past 25 years. This shows the dispersion which, in much of the dry tropics, is

so great that averages have little meaning. A further sheet shows irrigated areas and their proposed extensions, oases, and dams. This map has water balance diagrams (after C. W. Thornthwaite) for the same stations covered by the rainfall-temperature diagrams. The water balance diagrams are explained clearly and give some understanding of growing seasons and their lack. These two sheets contribute to the reader's understanding of the critical water problem in North Africa and the Middle East. There is a detailed strip map, with monthly river flow diagrams, of the Nile Valley and a similar map for the Tigris and Euphrates Valley.

There are further maps dealing with agriculture, minerals, industry, transport, population density, state of topographic mapping, and a historical survey.

The degree of detail on the agricultural maps varies with the available data. The Magreb, Egypt, Iraq, the Levant, and Turkey are covered by dot maps showing principal crops. Unfortunately, several of these maps are hardly readable, because they attempt to show on one sheet as many as three crops having largely overlapping distributions. This is a gross violation of the grammar of economic map making. There is a useful and less detailed sheet for the Sudan and only a listing of commodity production totals (from the Food and Agricultural Organization of the U.N.) for Iran, Ethiopia, Somalia, and the countries of the Arabian Peninsula.

There are maps showing oil production and producing fields as of 1957 and oil concessions as of 1958; a detailed map shows oil production in the Persian Gulf as of 1957. Over 20 industries are treated on five sheets in sufficient detail to bring out the meaningful regional differences. Air, rail, and water transport are handled on separate sheets. There is a detailed sheet of the Suez Canal and a flow diagram indicating the relationship of the canal to world shipping.

Population is treated by a dot map (one dot per 20,000 people) with names of peoples and principal tribes (Kurds, Nuer, and so forth) listed in their home areas. Urban areas are also indicated.

There is a final map which attempts to give a historical summary. For a land with the complex cultural background of the Middle East and North Africa, one map cannot be adequate. An entire atlas, *A Historical Atlas of the Muslim Peoples* [Roelvink, Cambridge Univer-

sity Press (1957)] has been devoted to the topic.

The supplementary notes and statistics are excellent. For nearly all of the commodities and industries, enough information is given to show production trends.

The title is perhaps modest. The *Oxford Regional Economic Atlas of the Middle East and North Africa* contains the general physical and economic background of the region plus more detailed treatment of the salient physical and economic landmarks. The information is sufficiently comprehensive for the reader to obtain a sound understanding of the principal resource patterns and problems of the Middle East and North Africa.

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Stratigraphic Principles and Practice. J.

Marvin Weller. Harper and Brothers, New York, 1960. xvi + 725 pp. Illus.

With the ever-increasing need for a rational synthesis and integration of the vast store of published factual data in stratigraphy, it is a timely task to review and to reappraise the fundamental principles and major concepts which constitute the stratigraphic discipline. It is also timely to advance the standards in methods and procedures of stratigraphic work in the field and in the office.

Marvin Weller has admirably accomplished this task in his new book *Stratigraphic Principles and Practice*. The text is a welcome contribution to the better understanding of stratigraphic problems, many of which still await solution. The book is well written and places proper emphasis on the application of principles, the consideration of concepts, and the interpretation of basic data; this is a marked contrast to the outmoded catalog-like presentation of the subject.

Controversial issues are treated with an objectivity that provides a stimulating challenge to students to think and to reason things out for themselves. The bibliographic references, given at the end of each chapter, are, for the most part, adequate, but the addition of a few more titles of original sources would be desirable.

The book is divided into four parts: The first, short part contains the "Introduction," "Development of stratig-

raphy," and "Geologic systems"; the second contains "Materials of stratigraphy"; "Stratigraphic bodies and relationships, including classification and nomenclature" is the third part; the fourth, the "Appendix," contains practical suggestions for field work and the preparation of reports. The text is well illustrated, containing 271 figures and many tables.

The historical approach in dealing with the development of stratigraphy is highly commendable, but it should not have been stopped with William Smith. The important contributions made by Lyell and other early investigators during the fruitful years of the middle of the last century are alluded to only briefly at various places in subsequent chapters.

Reference to "zonation" (in association with William Smith's name) as one of the fundamental principles that had been recognized at the beginning of the 19th century may be misleading, unless in this instance the author uses *zonation* to mean something different from the principle which was established during the years 1856-58 by Albert Opel.

The second part of the book, dealing with the materials of stratigraphy, calls for no special comments. Probably no two stratigraphers would agree on the extent to which the subject of sedimentology and the study of sedimentary rocks should be treated in a text on stratigraphy. The point of view may also vary from institution to institution, depending on curricula.

In general this part of the text is well balanced and well illustrated by drawings and diagrams based on recent original contributions.

The simplification of terminology in the discussion of unconformities, in part 3, is well supported by valid reasoning, although exception may be taken to the definition of an unconformity as a *stratigraphic plane*. *Stratigraphic plane*, if at all applicable, is only one element of an unconformity. An unconformity is a *geologic structure* or a structural relationship between two sets of rocks.

The subject of stratigraphic classification and nomenclature is well presented and is skillfully combined with the essential points of the Stratigraphic Code.

Weller is probably correct in saying that Füchsel in 1756 was the first to formulate the rudiments of the concept of the formation, but it should be pointed out that Füchsel *did not* introduce the term *formation*. He had

recognized distinctive lithologic units, such as the Muschelkalk and others, and these he called *series montana* or *Geburge* (probably this should have been spelled "Gebürge"). The misunderstanding, which has been perpetuated in geologic literature for many years, appears to stem from Zittel (1899, page 51) who inserted the term "(Formation)" as his own idea of the equivalent of Füchsel's *series montana*.

It may be also pertinent to note that the idea of the formation, with a connotation of time, as formulated by Humboldt and by his contemporary Buch, is different from the concept of the formation currently used in the United States and from the concept earlier expressed by Conybeare and Phillips and by Lyell. In the German geologic literature the term formation is applied to the concept which is now called a System, for example, *Die Juraformation*.

The discussion of biostratigraphic units, and, particularly, the distinction between biostratigraphic units and the time-rock units does not entirely clear up the points of contention among different schools of thought on that subject. Any fossiliferous unit is a biostratigraphic unit when it is analyzed for biostratigraphic data, such as composition of fauna (or flora), geologic age, paleoecology, paleobiogeography, dispersal of organisms, and the like. One, therefore, cannot agree with the author that biostratigraphic units "are wholly objective and not dependent upon interpretative considerations. . . ."

The use of the term *Series* for units which should be properly called *Stages* is, perhaps, a reflection of the transitory state of our period of stratigraphic thinking in the United States. The formational units called series in the sense of rock-units are commonly given "an" or "ian" endings and are, thus, "promoted" to time-rock Series. A greater uniformity in nomenclature would be achieved if the term *Series* were retained for subdivisions of Systems, such as Lower, Middle, and Upper.

The chapter on facies is comprehensive in scope and is amply illustrated with diagrams, graphs, and maps.

Some aspects of the limitation of paleontologic correlation, shown by the lack of correspondence in the stratigraphic occurrence of Jurassic ammonites in England and in France (Figs. 215 and 216), should be viewed in the light of more recent studies. The apparent anomaly in the succession (Fig. 215) has been explained by Spath (1938,

page 34) as being due to misidentification. As to "the other anomalies," according to Arkell (1956, page 104) "doubt is inevitably cast on them also."

The chapter on historical geology appropriately summarizes the objective of stratigraphy.

Students of stratigraphy, particularly beginners, will find the appendix with its practical suggestions for field work and for graphic presentation of results to be a very useful part of the book. The list of references to various manuals could be profitably enlarged by including Busk's *Earth Flexures, Suggestion to Authors*, and a few others.

Minor points, critically mentioned in the preceding paragraphs, do not detract from the general excellence of the book. *Stratigraphic Principles and Practice* merits favorable consideration for adoption as a text in stratigraphy.

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Biochemistry of Plants and Animals. M. Frank Mallette, Paul M. Althouse, and Carl O. Clagett. Wiley, New York, 1960. xiii + 552 pp. Illus. \$8.50.

In writing this textbook the authors had to cope with the difficult problem of presenting a vast amount of biochemical knowledge, in its many ramifications, to students of agriculture with limited preparation in modern physics, chemistry, and biology. Their solution is the best testimony of their broad scientific approach to complex subject matter and of their educational skill. I was surprised and impressed to find such advanced topics as the function of deoxyribonucleic acid and ribonucleic acid, nicotinamide adenine dinucleotide, adenosine triphosphate, biotin, gibberellic acid, auxins, and antiauxins discussed on an elementary level.

In the excellent chapter on mineral metabolism, radiation and radioisotopes are mentioned; in the very good chapter on feedstuffs, the use of antibiotics in livestock feeding has been given proper attention. Although written primarily to serve as a biochemical foundation for those studying the agricultural sciences, the book can also be recommended to all who wish to obtain a condensed review of the present status of biochemical knowledge.

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New Books

Mathematics, Physical Sciences, and Engineering

Pulp and Paper. Chemistry and chemical technology. vol. 1, *Pulping and Bleaching*. James P. Casey. Interscience, New York, ed. 2, 1960. 694 pp. Illus. \$19.50.

Reactions between Complex Nuclei. Alexander Zucker, Frederick T. Howard, and Edith C. Halbert, Eds. Wiley, New York, 1960. 328 pp. Illus. \$7. Proceedings of a conference (2-4 May 1960) sponsored by the American Physical Society and the Oak Ridge National Laboratory.

Reports on Progress in Physics. vol. 22, 1960. A. C. Stickland, Ed. Physical Society, London, 1960. 633 pp.

Rival Theories of Cosmology. A symposium and discussion of modern theories of the structure of the universe. H. Bondi, W. B. Bonnor, R. A. Lyttleton, and G. J. Whitrow. Oxford Univ. Press, New York, 1960. 76 pp. Illus. \$2.25.

Röntgenographische Chemie. E. Brandenberger and W. Epprech. Birkhauser, Basel, Switzerland, 1960. 272 pp. Illus. F. 32.

Seminar on Transformation Groups. Armand Borel. Princeton Univ. Press, Princeton, N.J., 1960. 251 pp. \$4.50. Contributions by G. Bredon, E. E. Floyd, D. Montgomery, and R. Palais.

Silicon and Its Binary Systems. A. S. Berezhanov. Translated from Russian. Consultants Bureau, New York, 1960. 283 pp. \$8.50. Originally published in 1958 by the Academy of Sciences of the Ukrainian SSR.

Silicon Carbide. A high temperature semiconductor. J. R. O'Connor and J. Smiltens, Eds. Pergamon, New York, 1960. 540 pp. Illus. \$12.50. Proceedings of a conference (1959) sponsored by Air Force Cambridge Research Center.

Some Ionospheric Results Obtained during the International Geophysical Year. W. J. G. Beynon, Ed. Elsevier, Amsterdam, 1960 (order from Van Nostrand, Princeton, N.J.). 413 pp. Illus. Proceedings of a symposium organized by the URSI/AGI Committee (Brussels, September 1959).

Space Rockets and Missiles. Raymond F. Yates and E. Russell. Harper, New York, 1960. 349 pp. Illus. \$3.50.

Spectra and Analysis. A. A. Kharkevich. Translated from Russian. Consultants Bureau, New York, 1960. 228 pp. \$8.75. Translated from the revised edition published by the State Press for Technical and Theoretical Literature, Moscow, 1957.

Spot Tests in Organic Analysis. Fritz Feigl. Translated by Ralph E. Oesper. Elsevier, Amsterdam, ed. 6, 1960 (order from Van Nostrand, Princeton, N.J.). 695 pp. Illus. \$13.25.

Tables and Nomograms of Hydrochemical Analysis. I. Yu. Sokolov. Translated from Russian. Consultants Bureau, New York, 1960. 85 pp. Paper, \$4.35.

Tables of Lommel's Function of Two Variables. E. N. Dekanosidze. Translated from Russian by D. G. Fry. Pergamon, New York, 1960. 499 pp. \$20.

Vibrations from Blasting Rock. L. Don Leet. Harvard Univ. Press, Cambridge, Mass., 1960. 149 pp. Illus. \$4.75.

Miscellaneous Publications

(Inquiries concerning these publications should be addressed, not to Science, but to the publisher or agency sponsoring the publication.)

American Midland Naturalist. Cumulative Index, (vols. 1-60). George R. Bernard, Ed. American Midland Naturalist, Notre Dame, Ind., 1958. 530 pp. \$4.25. Contains author, new genera and species, and subject indexes.

Education for Africans in Tanganyika. A preliminary survey. Betty George. U.S. Office of Education, Washington, D.C., 1960 (order from Supt. of Documents, GPO, Washington 25). 97 pp. \$0.40.

The Ending of Wilhelm Reich's Researches. Charles R. Kelley. Interscience Research Inst., Stamford, Conn., 1960. 19 pp. \$0.50. Kelley examines the Reich-orgone energy controversy and recounts his attempts to discuss, with responsible officials, the injunction obtained by the Food and Drug Administration to ban Reich's books and journal publications. Kelley says that he was unable to obtain an appointment with Mrs. Hobby who was the Secretary of Health, Education, and Welfare at the time.

Federal Funds for Science. No. 9, *The Federal Research and Development Budget, Fiscal Years 1959, 1960, and 1961.* National Science Foundation, Washington, D.C., 1960 (order from Supt. of Documents, GPO, Washington 25). 89 pp. \$0.50.

Labor Relations Policy in an Expanding Economy. vol. 333 of *Annals of the American Academy of Political and Social Science.* Marten S. Estey, Ed. The Academy, Philadelphia, Pa., 1961. 213 pp. Cloth, \$3; paper, \$2.

Large Radiation Sources in Industry. vol. 2. International Atomic Energy Agency, Vienna 1, Austria, 1960 (order from UNESCO Publications Center, New York 22). 447 pp. Illus. Paper, \$4.50. This is the second volume of the proceedings of a conference on the application of large radiation sources in industry and especially to chemical processes, which was organized by the Agency at Warsaw on 8-12 September 1959. Four major topics are covered: radiation and chemical reaction, special applications of radiation, radiation and food preservation, and economics of radiation processing.

A Monograph of the Nearctic Plagiolichaceae. Rudolf M. Schuster. American Midland Naturalist, Notre Dame, Ind., 1960. 434 pp. \$4. Papers reprinted from vols. 62 and 63, *American Midland Naturalist*.

Review of Fungal Diseases of Cotton in Egypt. Egyptian Reviews of Science, vol. 3. M. A. Mostafa. Science Council, Cairo, 1959. 55 pp.

Symposium: Speciation and Racialization in Cavernicoles. American Midland Naturalist, Notre Dame, Ind., 1960. 160 pp. \$2.50. Papers presented at the 1959 annual meeting of the AAAS, in a symposium sponsored by the National Speleological Society and the Society of Systematic Zoology.

United States Business Performance Abroad. No. 9, *The General Electric Company in Brazil.* Theodore Geiger. National Planning Assoc., Washington 9, 1961. 105 pp. Paper, \$1.

Reports

A Mechanism of Light Adaptation

Abstract. In the isolated retina of the bullfrog (*Rana catesbeiana*) illumination of one part of a ganglion cell's receptive field increased the light threshold (for response by that cell) not only in the illuminated part but also in the unilluminated parts of the field. Scattered light is insufficient to account for the effect. Apparently it depends on changes in the efficiency of excitation transmission along the neural pathways from photoreceptors to ganglion cell.

Visual thresholds rise on exposure to increased illumination (light adaptation) and fall on exposure to decreased illumination (dark adaptation). Five hypotheses have been advanced in explanation. The first, that these processes are due entirely to bleaching and regeneration, respectively, of rhodopsin, has been shown to be untrue (1), except possibly at high light intensities. The second, that changes occur in the spatial summation of light stimuli incident on the retina, has been found to account for only a 20-fold threshold change out of a 3000-fold total in the human being (2). The third, assuming similar changes in temporal summation, has not been adequately tested, but it is unlikely that it will account for any greater threshold change than the second. The fourth is that a rod consists of many compartments, each inactivated by the photolysis of any one of the molecules of rhodopsin in it—the rod's output activity being proportional to the number of photons absorbed in intact compartments (3). This would result in the threshold's being related, though not in inverse proportion, to the amount of rhodopsin present. The fifth is that the efficiency with which excitation is transmitted

from the receptors to the optic nerve is changed during light or dark adaptation. The last two hypotheses were tested over the lower 600-fold threshold change by the experiments described below.

In each experiment the excised retina of a dark-adapted bullfrog (*Rana catesbeiana*) was placed receptor side up in a moist chamber and supplied with a moistened mixture of 95 percent oxygen and 5 percent carbon dioxide. A microelectrode pierced down through the retina to contact the body or axon of a single ganglion cell. Its action potentials were amplified and presented on an oscilloscope and a loudspeaker. In contact with the underside of the thin glass cover slip forming the chamber's bottom was a metal diaphragm having a tiny opening. The chamber and electrode holder were mounted on a stage that was movable with respect to the diaphragm, and whose position could be determined within 5 μ by micrometer screws. Light from a tungsten filament lamp, of an intensity determined by a neutral density wedge, passed through an electromagnetic shutter, a system of lenses and mirrors, and the diaphragm, entering the retina in the natural direction from the ganglion cell side and forming an oval light spot about 100 by 160 μ at the receptors.

Threshold was tested with $\frac{1}{2}$ -second light flashes at 5-second intervals. Threshold was taken as that intensity which elicited three responses (discharge of action potentials) from the ganglion cell in four successive flashes. These responses are known to be rod-dominated (4). The retinal region (receptive field) in which illumination elicited a response was located. Micrometer screws at the left and right of the stage were set so that movement of the stage into contact with one or the other would direct the light spot onto either of two selected areas in the receptive field. One area was illuminated continuously for several minutes. Then the thresholds were measured alternately at the (previously) illuminated and the unilluminated areas to determine how much each had changed, and to follow their dark adaptation (5).

The unilluminated area, as well as the illuminated one, showed a rise in

threshold. To determine whether this was caused by light scattered from the illuminated to the unilluminated area, use was made of measurements taken previously on the same apparatus of the light-scattering properties of the frog retina (6). An upper bound was computed for the average intensity of light scattered from the illuminated area to the rods of the unilluminated area. Direct illumination of the latter with the average or a greater intensity produced a threshold rise which in nine out of ten areas so tested (in three different retinas) was less than the rise to be explained. In the tenth it was slightly greater. Since these upper bounds exceed the actual light scatter, these experiments showed that little, if any, of the threshold rise in the unilluminated area was caused by scattered light.

In the experiment illustrated in Fig. 1, area 1 was the most sensitive region of the receptive field, and area 2 was more peripheral by 350 μ , with 100 times higher threshold. Area 1 was illuminated for 10 minutes with 315,000 times its threshold intensity. This caused a greater rise in area 2's threshold than did the same illumination directed onto area 2. The same was true in three other

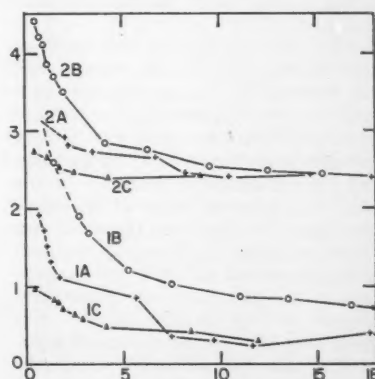


Fig. 1. Dark adaptation of illuminated and unilluminated areas in the receptive field of a frog's retinal ganglion cell after 10 minutes of illumination of one of the areas. Ordinate: common logarithm of the relative light intensity. Abscissa: minutes in the dark. Curves 1A and 2A, thresholds of areas 1 and 2, respectively, after illumination of area 2. Curves 1B and 2B, thresholds of areas 1 and 2, respectively, after illumination of area 1. Both illuminations were made with light of 5.5 logarithmic units relative intensity. Curve 1C, threshold of area 1 after illumination of area 1. Curve 2C, threshold of area 2 after illumination of area 2. Both illuminations were made with light of 3.5 logarithmic units relative intensity. For the first two illuminations the computed upper bound of light scatter from one area to the other was 2.3 logarithmic units relative intensity. Note that 1A exceeds 1C, and that 2B exceeds both 2C and 2A.

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should not repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper.

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to one 2-column figure (that is, a figure whose width equals two columns of text) or to one 2-column table or to two 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [Science 125, 16 (1957)].

central-peripheral pairs of areas so tested.

In another experiment, in a single receptive field the effect of illumination at the center was compared with illumination of three areas peripheral by various distances. The threshold rises evoked centrally by peripheral stimulation, and vice versa, did not decrease rapidly with increased separation (as would be expected if caused by scattered light), but remained roughly the same over the whole range of separations (300–810 μ).

For a fixed duration of light adaptation, it was found that $I_{st}/I_{st} \approx kI_0/I_{st}$; where I_{st} is the post-adaptation threshold (measured after 1 minute in the dark) and I_0 is the pre-adaptation threshold, both for the tested area; k is a constant; I_0 is the adapting intensity; and I_{st} is the pre-adaptation threshold of the illuminated area. If illumination and testing are done on the same area, I_{st} and I_{st} become the same. This relation held no matter which was the illuminated and which the tested area in the given receptive field. It held, and with the same constant of proportionality, for four receptive fields, all "on-off" type, each in a different retina, in which a total of 31 adaptations were measured.

These findings indicate that the fraction of excitation reaching the ganglion cell from illuminated receptors anywhere in the receptive field is reduced in proportion to the amount of activity just previously sent toward the ganglion cell from illuminated receptors in the same or a different region of the receptive field. The resultant threshold rise found on testing any group of receptors is not dependent on their previous exposure to light (and any consequent changes in their visual pigments), but apparently is a change in the efficiency of excitation transmission along the neural pathways to the ganglion cell (7).

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References and Notes

1. For a review of this question, see G. S. Brindley, *Physiology of the Retina and the Visual Pathway* (Williams and Wilkins, Baltimore, 1960), pp. 180–185.
2. G. B. Arden and R. A. Weale, *J. Physiol.* **125**, 417 (1954).
3. G. Wald, *Science* **119**, 887 (1954).
4. K. O. Donner and R. Granit, *Acta Physiol. Scand.* **17**, 161 (1949); R. Granit, *Sensory Mechanisms of the Retina* (Oxford Univ. Press, London, 1947), p. 269.
5. This experimental approach is based on one suggested by W. A. H. Rushton.
6. L. E. Lipetz, *Abstracts of Fourth Annual Meeting of the Biophysical Society* (1960), p. 25.
7. This work was supported by a research grant, B-1408, from the National Institute of Neurological Diseases and Blindness, U.S. Public Health Service, through a contract with the Ohio State University Research Foundation.

17 October 1960

Plaque Reduction, a Sensitive Test for Eastern Encephalitis Antibody

Abstract. Serologic surveys of vertebrates to determine rates of eastern encephalitis infection were made to discover the most likely disseminators of virus in nature. Of the techniques available, neutralization is the most specific, and antibody is known to persist for many years. This communication reports a fivefold increase in sensitivity of neutralizing-antibody detection by the application of a plaque-reducing technique.

Itoh and Melnick (1) were able to detect antibody to ECHO type 4 virus by plaque reduction when standard tube techniques failed to reveal it. They defined the titer of a serum as the highest dilution which reduced the number of plaque-forming units by 80 percent. The use of this method for detecting eastern encephalitis antibody was suggested by Henderson and Taylor (2).

Adequate numbers of sera, in adequate amounts, were not available for testing from natural infections; only 11 human sera, collected 1½ to 22 years after infection with the virus, were available. To induce infection, five wild rabbits, five crows, two blue jays, four pigeons, five chickens, five frogs, and four squirrels were inoculated subcutaneously with eastern encephalitis virus. All animals which became viremic produced plaque-reducing neutralizing antibody and maintained it throughout the 9 months of serial bleedings (group 1). The animals in which viremia was not demonstrated failed, with one exception, to produce antibody, and blood samples from these animals, together with samples from pre-inoculation bleedings, comprised the

controls (group 2). Blood samples from these various sources plus 91 samples from field specimens of birds and mammals (group 3) made a total of 229 sera examined in parallel by two methods.

Chick embryo tissue cultures were prepared, as described previously (3). The planting medium, Hanks-Eagle-pyruvate 1-percent fresh egg albumin (HEPA), was supplemented with 1-percent horse serum to obtain a continuous sheet of cells in 60-mm plastic petri dishes. After 48 hours of incubation the medium in tube cultures was replaced with "change medium" HEPA, buffered with tris hydroxymethyl amino methane (pH 7.8) (no bicarbonate and no serum). The planting medium was removed from the plates just before inoculation.

Sera were diluted 1:5, inactivated at 56°C for 30 minutes, and incubated for 1 hour at room temperature with an equal volume of eastern encephalitis virus at a dilution calculated to contain 200 TCID₅₀ per 0.1 ml. Two plates and two tube cultures were inoculated with 0.1 ml of each serum-virus mixture. After 1 hour of adsorption at 36°C, the plates were overlaid, without washing, with 4 to 5 ml of "change medium" containing 1 to 1.5 percent of agar. After 48 to 72 hours' incubation at 36°C, the plates were stained with neutral red (1:10,000) in saline.

The plaque-forming units of several control plates were averaged in each of nine experiments; the average number of units ranged from 25 to 80. In tube cultures, hemagglutination of goose red blood cells by supernatant fluids (4) served to differentiate specific viral cytopathogenic effects from other tissue-destroying factors, such as toxic sera.

Table 1. Detection of eastern encephalitis neutralizing antibody: results of tests by two methods, in parallel, of serum-virus mixtures. Group 1, sera ($N = 11$) from human beings who had recovered from eastern encephalitis, and sera ($N = 97$) from inoculated animals after viremia had been demonstrated. Group 2, sera from animals before inoculation, and after inoculation when no viremia had been demonstrated. Group 3, sera from field specimens (birds and mammals).

Plaque-reduction neutralization*			Tube-culture neutralization†			
Positive	Equivocal	Negative	Positive	Equivocal	Negative	Total
Group 1, infected						
82	16		18	11	53	82
			0	1	15	16
		10	0	0	10	10
Group 2, controls						
3‡	0		0	0	3	3
			0	0	0	0
		27	0	0	27	27
Group 3, unknowns						
7	2		0	2	5	7
			0	0	2	2
		82	0	0	82	82
Totals						
92	18	119	18	14	197	229

* Categories for reduction of plaque count of the serum-virus mixtures are as follows: (positive) 0 to 20 percent of the average count of plaque-forming units of virus controls; (equivocal) 21 to 30 percent; (negative) 31 percent or more. † (Positive) 2:2 cultures, no virus growth; (equivocal) 1:2 cultures, no virus growth; (negative) 0:2 cultures, no virus growth. ‡ Three blood samples from a single inoculated wild rabbit; presumably viremia was missed.

The following technical points contributed to success in the tests. (i) Replacement of tris buffer in the overlay with sodium bicarbonate (0.35 g/lit.) and incubation in 5-percent carbon-dioxide increased the contrast of staining and the size of the plaques. (ii) The volume of inoculum for test and control plates was always kept the same, since in pilot experiments multiples in excess of five of the standard inoculum (0.1 ml) gave a lower count of plaque-forming units than was expected; this was ascribed to the reduction in number of cell hits by virus particles with increasing depth of fluid. With the small volume of inoculum, a humid atmosphere during adsorption was essential to prevent destruction of the cell sheet by drying.

Of 92 sera found positive by the plaque-reduction technique, only 18 (20 percent) were found positive by the tube assay of the same serum-virus mixtures (Table 1). Sixteen of these positive tube tests were on sera which reduced the plaque-forming units to the lowest level—that is, strongly positive sera. The 11 sera collected from seven human beings who had recovered from eastern encephalitis were all strongly positive according to the plaque-reducing test, but only five were positive according to the tube test. The inefficiency of tube cultures in antibody detection is believed to be due to the high sensitivity of such cultures to a few unneutralized particles of infectious virus. Dissociation of virus from antibody in the fluid medium may be a factor.

Correlation of results of the plaque-reducing test with the history of the serum donor was good. There were no false positive results in these tests in the control group. Only four sera could be considered "false-negatives"—that is, sera in which the plaque-reducing test failed to reveal antibody when the animal had previously been shown to be producing antibody.

We hope in the future to get more accurate information, through the plaque-reducing method, on immunity to eastern encephalitis in human beings in endemic areas and in animals collected in the field (6).

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17 October 1960

Nondiscriminated Avoidance Behavior in Human Subjects

Abstract. College students were required to learn a plunger-pulling response to postpone the occurrence of a shock or to avoid the loss of a monetary reward. Marked individual differences in the response patterns appeared in the first hour and persisted through 20 hours of testing. These differences overshadowed those produced by moderate alterations in the schedule or value of the aversive event.

Since Sidman (1) described the experimental schedule in which each response postpones the occurrence of an aversive event, it has been used in numerous studies of rats, cats, monkeys, and pigeons (2).

Recently, Hefferline *et al.* (3) reported conditioning human adults to make a tiny, involuntary twitch of the thumb in order to turn off or postpone an aversive noise. Baer has used the same avoidance-escape schedule with preschool children (4) who worked to escape interruptions in the presentation of cartoons.

The subjects in this experiment were 33 paid volunteer college students. Two kinds of motivating conditions were used: under the shock-avoidance condition, the subject had disk electrodes strapped to the front and back of his forearm on the nonpreferred side. The aversive stimuli were alternating-current pulses of 30-msec duration which were individually adjusted to the highest level judged endurable (which ranged from 0.3 to 1.0 ma). Subjects at both ends of the shock current continuum described the shock as "a sharp pinprick." Under the coin-loss condition, the subjects were shown 100 pennies in a display magazine and told that all pennies remaining at the end of the session would be added to their base pay of \$1.50 per hour. The aversive stimulus under this condition was the disappearance of a penny from the magazine, with the accompaniment of a loud clang. Under both conditions the aversive events occurred at 20-second intervals unless the appropriate response was made.

Two Lindsley manipulanda (5)

protruded from the front of the fully enclosed relay rack that also served to support the penny magazine. Pulling and releasing the left-hand plunger was the correct response, while manipulating the right-hand lever was entirely irrelevant.

Six subjects were run for ½ hour under the shock-avoidance condition, followed by ½ hour under the coin-loss one, and five were run in the reverse order, coin-loss followed by shock-avoidance. The remaining 22 subjects were tested under the coin-loss condition only. The first 23 subjects were told only that something they could do in the experimental room would influence how many aversive stimuli were presented. The last 10 were told that the plungers on the front of the apparatus would control the occurrence of the aversive stimuli, but were not told how to use them.

Of the 33 subjects, 23 developed a stable avoidance response within the first hour. However, only nine achieved the most efficient pattern of responding in that (i) their rate of responding on the correct plunger approached three responses per minute, and (ii) the rate on the irrelevant plunger was zero. Of 11 subjects exposed to both loss of coin and shock as aversive stimuli, 82 percent developed an avoidance response; of those exposed to loss of coins only, 64 percent did so. The difference, not statistically significant, appeared to be due to a resurgence in exploratory behavior after the experimenter entered

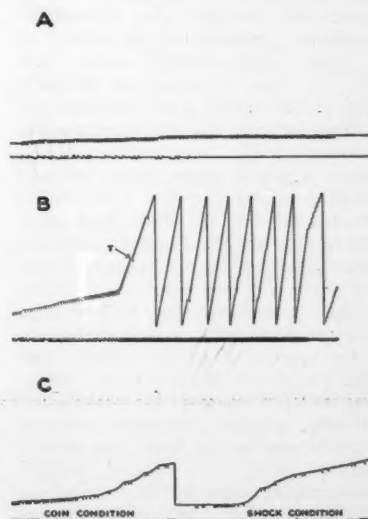


Fig. 1. Representative records from first hour of testing. Each response by subject moves pen vertically. Full excursion is 500 responses. Small pips on record indicate occurrence of aversive event—loss of coin in all cases but C. The horizontal line indicates responses on the irrelevant lever.

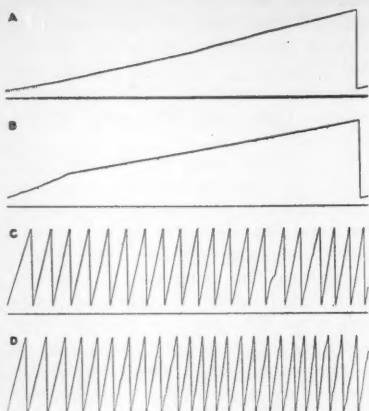


Fig. 2. Records of selected 2-hour test sessions from two subjects. A, 3rd session; B, 9th session of subject with lowest mean rate; C, 3rd session; D, 9th session of subject with highest mean response rate. The session previous to that shown in B required 12 responses per minute.

the room halfway through the period to give new instructions. On inquiry, 7 of the 11 subjects who experienced both conditions stated that losing money was the more distasteful, only three said the shock was more distasteful, and one was indifferent. Avoidance responses were developed equally often by those who were instructed to use the plunger and by those who were not. Those who were not so instructed sometimes displayed such bizarre behavior as standing in the corner or standing on the heads. The proportions of males and females who learned the avoidance response did not differ.

Three representative records from the first hour of testing are shown in Fig. 1. The record of an individual who did not develop an avoidance response is shown in Fig. 1A. Characteristically, some responses were made on each plunger during the first half-hour of the session, but all efforts were abandoned about midway in the session. Figure 1B shows a common pattern of abrupt change in response rate. Also common was the pause such as occurred at the point marked T in the record. Note that the irrelevant right-hand plunger was pulled throughout the session, and also that satiation phenomena appeared near the end of the hour. The individual of Fig. 1C showed initially overcomplex behavior that was later eliminated, but he continued to manipulate the irrelevant plunger throughout. Also of interest is his lack of generalization of the response between the two conditions; such a failure was the rule, occurring in five of six opportunities. Some individuals eliminated responses on the irrelevant

plunger, but maintained an inappropriate rate, while others achieved an appropriate rate but failed to eliminate the irrelevant responses. No subject developed the most economical response pattern within the first hour's training.

After the first experimental session, 10 subjects were selected at random to participate in 20 additional hours of testing, and seven of them completed the entire series of tests. The loss of coins was used throughout this series as the aversive event; to investigate the effects of variation in the length of test session, in the interval between loss of coins, and in the magnitude of each loss.

All these subjects acquired the avoidance response by the end of the second hour, although some persisted with inappropriate rates and responses on the irrelevant lever throughout the entire 20 hours of testing. Typically from the third session on, each subject entered the experimental room and commenced immediately to pull the plunger at his characteristic rate. Only one subject showed the so-called warm up phenomenon that is often encountered in rats working under this schedule. Records of the third and ninth testing sessions (during which the response-loss interval was 20 seconds, and each aversive event cost 2 cents) for the subjects with highest and lowest response rates are shown in Fig. 2. Differences in response rates between individuals far exceeded those produced by alterations in the experimental conditions. Mean response rates for subjects under all conditions ranged from 6.21 to 119.8 per minute. In contrast, the median responses per minute for the three conditions of coin value were: 2 cents, 7.91; 10 cents, 8.22; and 50 cents, 8.88. The interval between a response and the loss of the next coin had a somewhat greater influence: at a 5-second interval the median rate was 22.84 responses per minute (12 was the minimum rate to protect all coins). Rates for the 20- and 80-second intervals were 4.46 and 3.06 respectively.

The basis for the large individual differences observed in the performance of nondiscriminated avoidance behavior by human subjects is now being investigated in this laboratory (6).

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16 December 1960

Electroretinogram in Response to X-ray Stimulation

Abstract. The retina of the grass frog, *Rana pipiens*, responds to flashes of high-intensity x-rays and produces an electroretinogram indistinguishable in form from the electroretinogram produced in response to light stimulation at low and intermediate intensities. At higher intensities the form changes and, for maximal responses, the electroretinogram in response to x-rays shows a lower amplitude and a longer latent period than that in response to light. The prolonged latent period indicates additional intermediate reactions for the x-ray response.

Invisibility is generally emphasized as one of the properties of x-radiation (1). The ability of x-rays to evoke some sort of retinal response, however, has been known from the fact that, in early years, men looked into x-ray beams and reported various visual sensations. Once the harmful nature of x-rays was recognized, this activity was suddenly curtailed.

Two successful attempts to produce electroretinograms by x-rays have been reported in the literature. Himstedt and Nagel (2) showed records from frogs and birds which indicate little more than some sort of electrical disturbance caused by x-rays; these records bear little resemblance to the electroretinogram as recorded today, in response to light, with modern equipment. Elenius and Sysimetsä (3) gave a brief report on low, threshold responses in human subjects suffering from cataracts.

Attempts to produce an electroretinogram in response to x-rays usually fail, due, apparently, in large part to inability to stimulate the retina with intense, quick flashes of high-energy x-rays. In the research reported here the difficulty was overcome with the experimental setup shown in Fig. 1. The high-intensity beam was built up, while the 1/2-in. lead shutter protected the eye of the frog from the beam. Slits of various widths in the lead shutter were passed over the eye, by remote control, much as a focal-plane shutter operates in a camera. The movement of the shutter gave exposure times proportional to the width of the slit and the speed of movement of the shutter. The duration of the exposure was monitored

by a photoelectric cell, sensitive to x-rays, placed in such a position that the beam of x-rays struck the cell at precisely the same time that it struck the eye. The whole eye was exposed to the x-ray beam.

A General Electric No. 1493 bulb, the source of light, was mounted inside a light-tight box, together with reflector, condensing lenses, and projecting lenses. An Alphax heavy-duty synchromatic shutter (Wollensak) was mounted on the front of the box. A small front-surface mirror, placed above the animal just outside the path of the x-ray beam, directed the horizontal light beam into the eye and provided total, uniform illumination of the eye. The instruments controlling the intensity of the light source were operated from an adjacent control room. The opening and closing of the shutter were remotely controlled by means of a shutter release with synchronizing circuits for triggering the oscilloscope and accessory photographic equipment. The output of the lamp was calibrated by reference to a standard lamp obtained from the National Bureau of Standards. The beginning and end of the light stimulation were indicated by the signal from a photocell mounted above the animal in a position such that the light passing through the mirror fell on the cell.

The animal was supported on a block of Styrofoam, which had been carved to fit the shape of its body. This block was fitted in the plastic container, to which water was added to keep the animal moist during the course of the experiment. Not evident in the figure is the fact that the animal was restrained in order to avoid the possibility of movement, which might interfere with the alignment of the eye relative to the x-ray and light beams. Shielded leads from the two electrodes in the animal were taken to a Tektronix type 122 pre-amplifier. The response was displayed on one beam of a Tektronix type 502 dual-beam oscilloscope, the signal from the photocell was displayed on the other beam, and the traces were recorded photographically with a Grass Kymograph camera. The information obtained from the oscilloscope was supplemented by concomitant recording from a Grass Model III-D electroencephalograph; two additional leads were taken from the electrodes in the animal to this instrument, as well as leads from the photocells.

Records were made from animals in which the cornea and lens had been removed and in which an electrode (either Ag-AgCl or 0.005-in. platinum-iridium wire fused into the tip of a small glass capillary tube) had been placed in the vitreous humor. More commonly, in view of the greater stability of the preparation, records were

made from the intact eye. Contact with the eye was made with a small stainless steel needle or with a sealed-wick-electrode assembly, shown in Fig. 2. The wick was placed in contact with the

surface of the eye, at the periphery, so as not to interfere with the light or x-ray beam. Sealed-wick assemblies of this type posed no problem of drying for periods in excess of 8 hours. The

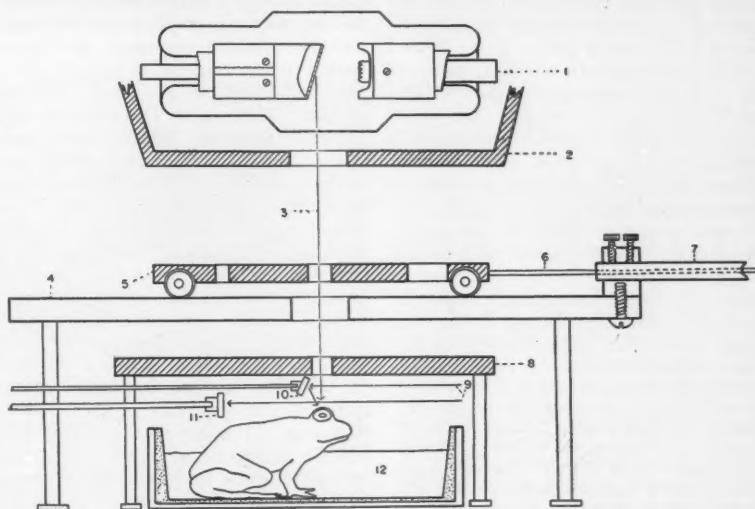


Fig. 1. Apparatus used for stimulation with light or x-rays, or both: 1, x-ray tube; 2, lead shield of x-ray tube; 3, x-ray beam; 4, track and support for lead shutter; 5, lead shutter; 6, shutter control shaft; 7, housing for control shaft; 8, lead shield over animal, with hole of same diameter as eye of animal; 9, light beam; 10, front-surface mirror; 11, photoelectric cell to record light signal; 12, plastic container with animal in water. Connections between animal and recording equipment are not shown. The photocell for recording x-ray signal is described in the text.

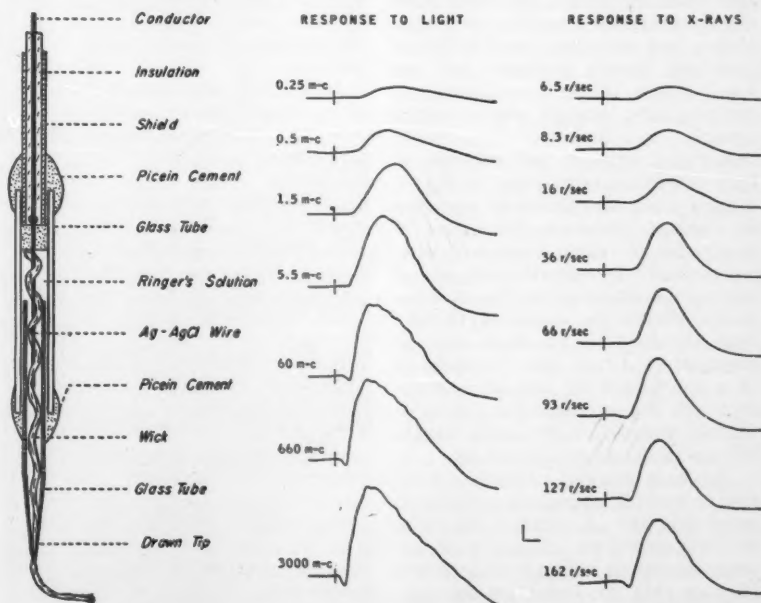


Fig. 2 (left). Wick electrode with sealed reservoir, designed to prevent leakage and permit use for extended periods of time. Fig. 3 (right). Electroretinal responses to light flashes of 0.08-second duration and intensities from 0.25 to 3000 m-ca, and to x-rays of 0.04-second duration and intensities from 6.5 to 162 r/sec. All responses are from the same animal during the same experiment. Calibration values: 150 μ v and 100 msec. The duration of x-ray stimulus used here exposed the eye to a minimum of x-ray damage yet produced maximal responses at the higher intensities.

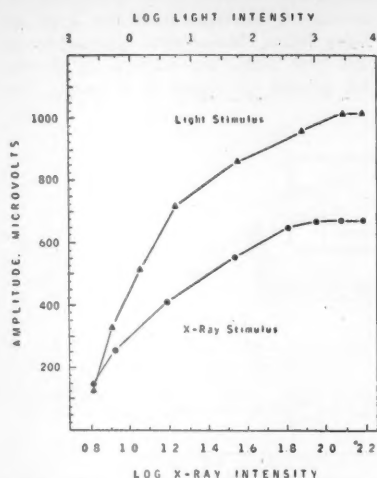


Fig. 4. Mean amplitude of *b*-wave in the on response to x-rays and to light, plotted as a function of the logarithm of light intensity in meter-candles and of x-ray intensity in roentgens per second. Duration of stimulus as in Fig. 3. The values indicate that a maximal response was obtained in both situations. Values are based on experiments involving 35 animals.

indifferent electrode in all cases was placed in contact with the skin over the nose. It was possible with this arrangement to record responses to light and responses to x-rays from the same animal under identical conditions without disturbing the assembly, since stimulating and recording equipment was controlled from a shielded room that was adjacent to the room containing the x-ray tube, the light source, and the animal.

A typical series of "on" responses to light and to x-rays is shown in Fig. 3, ranging from near-threshold responses to maximal responses obtainable for that particular retina. There is a striking similarity between the two sets of responses reproduced in Fig. 3, especially between the responses to light from threshold to 1.5 m-ca and the responses to x-rays from threshold to 66 r/sec. Lest it be concluded, therefore, that the mechanism of action of the two stimuli are the same, certain differences should be pointed out.

The mean maximal amplitude of the *b*-wave from 35 animals in response to x-rays was 665 μ V, whereas the mean maximal amplitude obtained from the same animals in response to light was 1010 μ V (Fig. 4). Increasing the magnitude of the stimulus in either case did not increase the amplitude beyond these maximal values. It is remarkable that the magnitude of the stimulus necessary to evoke the responses shown in Fig. 2 covered a 12,000-fold range for light, whereas the range for x-rays was only

25-fold. This point is emphasized in Fig. 4 by the different logarithmic scales for light intensity and for x-ray intensity.

The latent period for the response to x-rays in Fig. 2 varied from 135 msec for the maximal response to 190 msec for the minimal response; the latent period for the response to light, by contrast, varied from 60 msec for the maximal response to 150 msec for the minimal response. That Elenius and Sysimetsä did not detect a difference in the latent period of the two responses is probably due to the fact that they considered only a threshold response. At such low levels, the latent period of the two responses does not differ as greatly as at higher amplitudes, although, in the work under discussion, considerable difference was found even at the lower amplitudes. In studies on 35 animals, for example, the mean latent period for 120- μ V responses to x-rays was 181 msec, whereas for comparable responses to light it was 140 msec. The mean latent period for maximal responses to x-rays for the same animals was 129 msec, whereas for maximal responses to light the latent period was 71 msec.

The period of latency of the two responses is of considerable significance. Differences in latency suggest different mechanisms in the interaction between the photoreceptors and light, on the one hand, and the photoreceptors and x-rays on the other. Absorption of x-ray photons by the rods is apparently responsible for the electroretinogram. This assumption is based on two lines of evidence. First, no electroretinogram in response to x-rays could be elicited in this laboratory from the horned toad, an animal which lacks rod vision. Second, when the logarithm of the brightness of light necessary to produce a constant response is plotted as a function of time in the dark, the resulting curves for dark adaptation show a break which characteristically occurs during the early stages of adaptation. This break is similar to breaks which have been reported in curves for dark adaptation in human beings and which have been shown to indicate a shift from cone to rod function. Such a break was observed in the response to light but not in the response to x-rays. In view of the results reported here, we propose that, in some way analogous to the manner in which the rods react with visible light, the pigment of the rods, rhodopsin, absorbs x-ray quanta, undergoes chemical change, and leads to excitation which produces the electroretinogram. In this sequence of events the delay, and hence the difference in the response, is to be found in the chemical change involved in the bleach-

ing of rhodopsin. It is suggested that the reaction of radicals produced by x-rays (4) is involved in the chemical change (5).

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Micromanipulation in Control and Handling of *Zygiella x-notata* as an Experimental Animal

Abstract. The spider *Zygiella x-notata* may be brought under direct control analogous to that of the common laboratory animals for an important group of experimental investigations on the nerve, muscle, or secretion of digestive glands. Without anesthetics, chilling, or damage the animal can be fixed for prolonged periods and microinstruments (which include feeding pipettes), positioned by a standard micromanipulator.

The spider *Zygiella x-notata* has been used as a sensitive biological test animal for a number of psychopharmacologic and hallucinogenic drugs (1). Characteristic disturbances in web-building activities and patterns reflected the effects of the drugs on the central nervous system of the animal. Important applications of the test to body fluids of man have been made in the search for hallucinogenic substances in schizophrenia by Witt and Weber (2).

Administration of psychotropic substances has been either by direct injection (with a high mortality due to irremediable chitinous damage), or by the ingenious indirect technique of Wolff and Hempel (3); the latter consisted in the injection of the drug dissolved in sugar solution into the abdomen of a desiccated fly which was weighed and thrown on the web, which was then vibrated by a tuning fork. When the spider had accepted this artificial prey the latter was again weighed to determine the amount of the drug taken.

The present investigations were designed to explore the possibility of direct dosage without injury in this small

(5 to 6 mm) animal and the placing of microinstruments before and after the administration of various substances, including those of the psychopharmacologic and hallucinogenic group (Fig. 1). A method was devised to maintain the animal in a position suitable for

operations for prolonged periods without anesthetics, chilling, or damage.

Before fixation of the animal a small drop (approximately 1 to 2 mm³) of collodion-amyl acetate was placed on a microscope cover slip; this was allowed to thicken for 20 to 30 seconds. The

cover slip was inverted onto the dorsal surface of the abdomen of the spider and held down for a few seconds. The cover slip was then turned over to bring the ventral surface of the animal under the microscope to allow access for the micromanipulator instruments, which could be positioned quickly and accurately by the standard micromanipulator (Leitz) equipped with three instrument carriers; a stereo-binocular microscope facilitated observation. The animal could be maintained in position in this way for several days without any ill effects. Outbursts of activity took place, but the spider also remained immobile for long periods. Micro-salt-bridges made from glass capillaries, the terminal points being filled with agar (4) or 25 μ microelectrodes (5), may be applied for nerve (or muscle) studies; capillary tubing with a flexible taper of 2 to 3 mm and a diameter of 0.1 to 0.2 mm (with a tip diameter of 20 to 30 μ) permitted movement without breakage. Though insertion of micro-salt-bridges (as distinct from injection) at the side of the thorax resulted in about a 50-percent mortality (8 in 15 animals), the remainder survived for approximately 24 hours, long enough for most investigations into electrical changes.

In order to sample digestive fluids or to administer solutions, micropipettes with a mean diameter of 0.1 mm in the terminal 1 mm were suitable. Samples were obtained on contact by capillarity, and variations in secretory activity were observed directly under the microscope and recorded photographically (Fig. 1). For this a 35-mm camera provided with a mirror reflex housing, viewing magnifier, and bellows extension fitted with a 25-mm Micro Summar (Leitz) was used; an electronic flash unit (Zeiss) combined with fast film enabled satisfactory photographs to be obtained. Delivery of the contents of a pipette tip (drawn up in controlled amounts by capillarity) was effected by the micromanipulator syringe; contents in contact with secretory fluids in a pipette tip over 20 μ in diameter may be easily expelled. Pipettes were marked for measured volumes and delivered quantities of the order of 0.01 mm³. By such means the effects of feeding and the injection of possible test substances on the secretion of digestive glands may be estimated.

The techniques described may thus be capable of extension to further experimental studies on the reactions of these animals to substances affecting tissue components other than those of the central nervous system.

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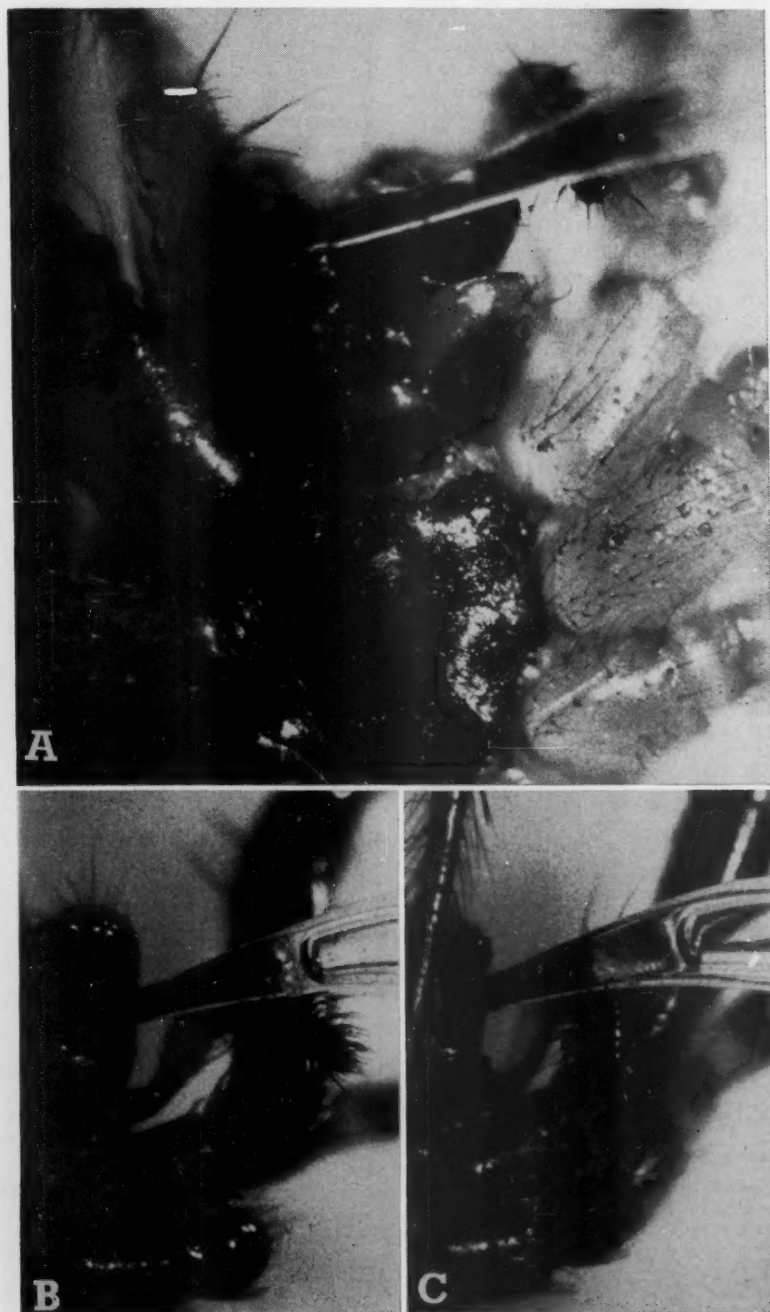


Fig. 1. (A) Typical sampling and feeding pipette in relation to spider ($\times 48$ at $f/24$); electronic flash. (B) Pipette in normal animal filling by capillarity to approximately 0.1 mm³ ($\times 32$ at $f/24$); electronic flash. (C) Same pipette as (B) 2 minutes later ($\times 32$ at $f/24$); electronic flash.

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- 6 October 1960

Multi-Resistant *Aedes aegypti* in Puerto Rico and Virgin Islands

Abstract. The Isla Verde, Puerto Rico, laboratory colony, highly resistant to DDT and dieldrin in 1959, became even more so by 1960; resistance to organic phosphates was also greater than before. In laboratory tests Bayer 29493 was best for killing resistant larvae and adults. It is improved with piperonyl butoxide at the ratio of 10:1.

The theory that *Aedes aegypti* can be resistant to DDT or dieldrin but not to both (1) was disproved by the Isla Verde strain (2, 3). This dual resistance occurs not only in the laboratory but along the whole north coast of Puerto Rico (4). When there is danger of the spread of yellow fever in the Caribbean (5), the presence of vigorous races recalcitrant to control has ominous implications for public health. To find an insecticide for overcoming resistant strains is imperative and for this purpose the Isla Verde strain is obviously more useful than the susceptible strains of most laboratories (6). The original toxicological tests (2) on this strain were made from March through July 1959 on about the F_{10} generation of a colony started in November 1958. By July 1960 the colony was estimated to be at the F_{30} generation after continuous inbreeding. At that time, in the field not far from the original site, more specimens were collected (7), and the F_1 and F_2 generations were obtained for tests to com-

pare with the original data. In 1959, 2.5 parts of malathion, diazinon, and dipterex per million gave 100 percent mortality; therefore, this concentration was used as a standard (8). Table 1 shows that the colony became even more resistant to DDT, lindane, dieldrin, and chlordane; in the field, except for lindane, the same high resistance occurs. As larval resistance to the chlorinated hydrocarbons increased in the colony, so did the resistance to the organic phosphates, but field resistance to the latter was not so marked. Resistance developed also to Bayer 21/199, the best larvicide in 1959. For specific use in mosquito control, Bayer 21/199 has been replaced by the manufacturer with Bayer 29493 (9), which is more effective against adult mosquitoes. Bayer 29493 was the most toxic in our tests and was made more so by synergism with piperonyl butoxide (10) at the ratio of 10:1 rather than the reverse ratio (11).

To prove further the resistance to organic phosphates, tests were made on the Isla Verde colony larvae at 0.5 part per million (ppm). In 1959 (2) dipterex, diazinon, and malathion only gave 72, 74, and 85 percent dead, and the same for dead plus moribund mortality; Bayer 21/199 gave 87 and 100 percent mortality. In 1960 the results were as follows (average of two replicates, dead and dead plus moribund mortality): Bayer 21/199, 65 and 100 percent; dipterex, 5 and 37 percent; malathion, 41 and 68 percent; diazinon, 34 and 73 percent; Bayer 21/199 plus piperonyl butoxide (10:1), 64 and 100 percent; Bayer 29493, 80 and 100 percent; Bayer 29493 plus piperonyl butoxide (10:1), 92 and 100 percent.

Females of the Isla Verde colony, which were exposed for 1 hour to bond paper impregnated with the following concentrations of insecticides at the rate of 3.6 mg/cm², gave the following

Table 2. Percentage mortality of *Aedes aegypti* fourth instar larvae of a colony (F_{3-4}) from material collected at Christiansted, St. Croix, in October 1959 (average of two replicates, dead and dead plus moribund).

Insecticide	0.5 ppm		2.5 ppm
	Dead	Dead plus moribund	Dead*
DDT	77	88	90
Lindane	45	77	95
Dieldrin	33	45	88
Malathion	66	88	95
Diazinon	60	78	95
Bayer 29493	92	100	85

*Dead plus moribund, 100 percent mortality for all.

percentage mortalities after 24 hours (average of two replicates): 4 percent DDT, 81 percent; 4 percent dieldrin, 47 percent; 3 percent Bayer 21/199 alone and with piperonyl butoxide (10:1 and 1:10), 18 to 22 percent; 0.4 percent malathion, 100 percent; 0.1 percent diazinon, 100 percent; 0.1 percent Bayer 29493, 100 percent; 0.05 percent Bayer 29493 plus piperonyl butoxide (10:1), 100 percent.

That DDT-dieldrin resistance already occurs in another island of the Caribbean was evident from tests on a St. Croix strain (12). Table 2 indicates moderate resistance to all insecticides listed except Bayer 29493. The lack of complete mortality with DDT and dieldrin at 0.5 ppm with this strain must be considered in relation to 100 percent mortality of susceptible strains at 0.02 ppm of these insecticides. It is likely that in about a year's time the same high resistance of Puerto Rico strains will occur in St. Croix, if DDT continues to be used there.

In conclusion, the following points are emphasized: (i) DDT-dieldrin resistance is not simply a laboratory phenomenon but is general in Puerto Rico and perhaps in other islands of the Caribbean where DDT resistance has been reported. (ii) A DDT-dieldrin resistant strain under the conditions of our laboratory did not lose its resistance after 18 months' colonization (13), but in fact became more resistant. (iii) The evidence is against the idea that genetic differences separate resistance to insecticides into distinct types.

IRVING FOX

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School of Tropical Medicine.

University of Puerto Rico, San Juan

References and Notes

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5. I. Fox, *Mosquito News* 18, 124 (1958).
6. This work was supported partly by research

Table 1. Percentage mortality of *Aedes aegypti* fourth instar larvae, Isla Verde, P.R., strain after 24 hours of exposure to insecticides at 2.5 ppm (average of four replicates, dead only). The effect of 18 months of colonization is compared with data from field material.

Insecticides	Laboratory colony		Field
	1959 (F_{10})	1960 (F_{30})	1960 (F_{1-3})
DDT	62*	25†	20†
Lindane	77*	30*	67*
Dieldrin	77*	0†	6†
Chlordane	25†	0†	2†
Dipterex	100‡	55§	94‡
Malathion	100‡	64§	94§
Diazinon	100‡	62‡	96‡
Bayer 21/199	100‡	58‡	97‡
Bayer 21/199 + piperonyl butoxide (10:1)		90‡	96‡
Bayer 21/199 + piperonyl butoxide (1:10)		97‡	55‡
Bayer 29493		91‡	94‡
Bayer 29493 + piperonyl butoxide (10:1)		100‡	100‡
Bayer 29493 + piperonyl butoxide (1:10)		95‡	36‡

Dead plus moribund: *79-89 percent; †0-44 percent; ‡100 percent; §98-99 percent.

grant No. RG-7152, Division of General Medical Sciences, U.S. Public Health Service, and partly by the Puerto Rico Department of Health.

7. Larvae and pupae were taken by Michel Guion from a boat on 22 July 1960 at the Yacht Club, Boca de Cangrejos, Isla Verde, P.R.
8. As in previous tests 20 fourth instar larvae in 200 ml of solution in cardboard disposable containers were used (4). To obtain dilutions a previous scheme (2) was modified to involve only two tubes. Thus for Bayer 29493: tube 1, 1 gram 25 percent wettable powder plus 24 ml distilled water; therefore each milliliter contains 0.01 g. Bayer 29493. Tube 2, 1 ml of tube 1 plus 99 ml water; therefore each milliliter contains 0.0001 g. To obtain 2.5 ppm (0.00025 part per 100), add 5 ml of tube 2 to 195 ml water; and for 0.5 ppm (0.00005 part per 100) add 1 ml of tube 2 to 199 ml water.
9. Bayer 29493 was obtained from the Chemagro Corporation, P.O. Box 4913, Hawthorn Road, Kansas City 20, Mo. It is a 25 percent wettable powder, O-O dimethyl O-[4-(methylthio)-m-tolyl] phosphorothioate, 25 percent; inert ingredients, 75 percent.
10. We thank Dr. W. E. Dove, Fairfield Chemical Division, P.O. Box 1616, Baltimore, Md., for piperonyl butoxide.
11. The value of a low ratio of synergist to toxicant has also been indicated in the case of Sevin and Sesoxane against resistant houseflies by M. E. Eldefrawi, R. Miskus, and W. M. Hoskins [Science 129, 899 (1959)].
12. Larvae and pupae were collected by Arthur H. Boike, Jr., from rain barrels in Christiansburg, St. Croix, V.I., 1 Oct. 1959.
13. R. W. Fay, Proc. New Jersey Mosquito Exterm. Assoc. 46th Meeting, 1959, p. 180.

25 October 1960

Uterotrophic Action of the Insecticide Methoxychlor

Abstract. Dusting of rats and mice, as well as oral treatment with the insecticide methoxychlor, produced uterine weight increase in these rodents. Ablation of the ovaries, adrenals, or pituitary did not alter this effect, thus indicating a direct trophic action of this agent on the uterus. It is apparent that the application of this insecticide to animals used for hormonal experiments introduces an additional variable.

During the past several months, marked uterine stimulation of unknown origin in immature female mice which had been obtained for use in hormone bioassay has been observed in this laboratory. After extensive examination and bioassay of diets, bedding, and several types of insecticide used in the animal production area, it was determined that one of the insecticide powders used for ectoparasite control contained the agent responsible for the uterotrophic effect. That this effect was not mediated through the ovaries was demonstrated by the marked uterine stimulation and concomitant vaginal opening induced in ovariectomized, immature mice and rats 3 days after these animals had received a single dusting with the insecticide. Each of the components of the insecticide was then tested by the dusting procedure and it was established that technical methoxychlor, an ingredient present at a level

of 1.91 percent, produced the effects observed in the female genital tract.

In a series of quantitative studies that followed, graded doses of technical methoxychlor (1), in sesame oil solution, were administered orally to groups of ovariectomized mice (Table 1). The data indicate that technical methoxychlor stimulates uterine weight increase in the mouse. Similar data were obtained in the rat at higher dose levels. An unusual effect was noted in the vaginal cytology of methoxychlor-treated mice. Instead of the typical cornified vaginal smear induced by 3 days of estrogen treatment, the smear was characterized by large numbers of leukocytes. Continued treatment resulted in vaginal cornification. However, in the rat, treatment with the compound resulted in vaginal cornification although occasional leukocytes were seen. Because of the extremely weak activity of methoxychlor when compared with estrone on the basis of weight increase in the uterus of the ovariectomized mouse (0.02 percent or less), the possibility that the insecticide might act indirectly through the metabolic pathways of the adrenal cortex was investigated. However, uterotrophic effects produced by oral treatment with technical methoxychlor in adrenalectomized, ovariectomized rats (Table 1) did not differ from those observed previously in ovariectomized animals. Experiments carried out in female hypophysectomized rats further demonstrated that methoxychlor acts directly on the uterus rather than by way of anterior pituitary hormones (Table 1).

In order to compare the pituitary depressant with the uterotrophic potency of methoxychlor, its action on the anterior pituitary gonadotrophic response of the rat ovary was also tested in parabiotic rats. In castrated female and intact female rats placed in parabiosis at 28 days of age, a 30-mg total dose of technical methoxychlor, given daily by stomach tube for 9

days, resulted in a mean ovarian weight of 16 mg (six parabiotic pairs) as compared with a mean of 104 mg for untreated controls (five parabiotic pairs). Thus, in common with the estrogens and related compounds, this substance blocks the gonad-stimulating action of the anterior pituitary. This inhibitory effect may clarify earlier unexplained findings (2) of extraordinarily small tests in experimental rats (pair-fed) maintained on a diet containing 1-percent methoxychlor.

The known adrenocorticolitic effects of related insecticides such as DDD (3) suggested the possibility that methoxychlor might alter adrenocortical secretion. In two adult mongrel dogs treated with this technical material in daily oral doses of 200 mg/kg for 15 days, there was no unusual deviation from the normal range of values for adrenal venous 17-hydroxycorticoid secretion as measured by Porter-Silber chromogens. Moreover, no distinct morphological changes in the adrenal cortex were noted.

Highly purified *p,p'*-methoxychlor was also assayed for uterotrophic effects in the rat and mouse. This isomer was only half as active as the technical product in the rat and was much less potent in the mouse. Anisole, one of the starting materials in the synthesis of technical methoxychlor has been reported to have estrogenic activity (4). In view of this report, anisole was considered as a possible contaminant of the technical material. However, when anisole was administered orally to immature, ovariectomized mice in total doses of 15 mg (5 mg daily for 3 days), there was no effect on uterine weight.

These findings indicate that an unidentified isomer or contaminant of technical methoxychlor is responsible in part for the uterotrophic effect (5).

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Table 1. Uterotrophic effects of methoxychlor in the mouse and rat. Technical methoxychlor in sesame oil solution was administered daily for 3 days by stomach tube. Controls received sesame oil only. Body and uterus weight: mean and standard deviation. NIH general-purpose strain mice and Sprague-Dawley rats were used in these studies.

Animals (No.)	Total dose (mg)	Operative procedure	Final body wt. (g)	Uterine wt. (mg)
<i>Mouse</i>				
9	0	Ovariectomy	9 ± 1	5.2 ± 0.6
10	0.5	Ovariectomy	10 ± 2	11.3 ± 3.3
9	1.0	Ovariectomy	9 ± 1	19.4 ± 3.7
10	5.0	Ovariectomy	10 ± 2	34.5 ± 6.7
<i>Rat</i>				
10	0	Ovariectomy plus adrenalectomy	55 ± 4	24 ± 5
10	20.0	Ovariectomy plus adrenalectomy	54 ± 6	70 ± 5
10	0	Hypophysectomy	73 ± 4	17 ± 2
10	20.0	Hypophysectomy	70 ± 5	58 ± 4

References and Notes

1. The sample used was ESA reference standard methoxychlor consisting of 1,1,1-trichloro-2,2-bis(*p*-methoxyphenyl)ethane (89.5 percent) plus other isomers of methoxychlor and related compounds (10.5 percent) obtained through the courtesy of Dr. E. E. Fleck, U.S. Department of Agriculture.
2. C. H. Hodge, E. A. Maynard, J. F. Thomas, H. J. Blanchet, Jr., W. G. Wilt, Jr., K. E. Mason, *J. Pharmacol. Exptl. Therap.* **99**, 140 (1950).
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5. The technical assistance of Donald Barber is gratefully acknowledged.

25 October 1960

Toxoplasma from the Eggs of the Domestic Fowl (*Gallus gallus*)

Abstract. Toxoplasmata of varying grades of virulence were isolated from eggs laid by clinically asymptomatic hens and from their internal organs. The strains so recovered were identified as *Toxoplasma gondii* by morphological, serological, cultural, and pathogenic criteria. These findings strongly suggest that toxoplasmosis may be contracted through the eating of raw or undercooked infected eggs.

Except for the report of Biering-Sorensen [cited by Siim (1)], who observed pseudocysts of *Toxoplasma* in the ovaries of naturally infected hens, indicating the possibility that eggs from such birds might be infected, we have been unable to trace any annotation referring to the isolation of the parasite from the eggs of the domestic fowl in the vast literature on toxoplasmosis, which now lists more than 2500 titles. Inasmuch as rapid clearing of tissues occurred in laying hens which received very heavy inocula, it seemed unlikely to Jones *et al.* (2) that the presence of *Toxoplasma* in the eggs of the hens would be anything other than an occasional finding. In view of the diver-

gent behavior of *Toxoplasma* in natural and experimental infections in chickens (2, 3), the problem of its localization in the eggs of naturally infected hens deserved a thorough study, which was undertaken by us during the course of our recent investigations into an enzootic of toxoplasmosis of fowls at one of the poultry farms in India.

Four of 42 eggs that have been screened to date were found to be infected, and extracellular and cyst forms of *T. gondii* were observed (Fig. 1) in scrape-smears of the chorioallantoic membrane. The identity of the parasite with *T. gondii* was confirmed by its transmission to mice and by serological tests. Surprisingly, none of the hens that laid these infected eggs had antibodies in their sera detectable by dye test, complement-fixation, precipitation, and indirect haemagglutination procedures. However, complement-fixation inhibition tests gave values ranging from 1:32 to 1:128.

Toxoplasmata were recovered from the diaphragmatic muscle, liver, brain, and ovaries of these asymptomatic hens when they were killed 2 weeks later. At necropsy, no gross lesions were seen in any of the internal organs but, interestingly, numerous cysts were demonstrated in crush-smears of the diaphragmatic muscle, liver, brain, and ovaries (Fig. 2) but not from spleen or lungs.

Immunologically, the isolates from laying hens were found to be identical with but pathogenetically different from the strains recovered from eggs. The egg-strains proved to be of low virulence for mice, and extracellular forms (Fig. 3) were detected in the peritoneal exudate of infected mice only by the third blind serial passage. The toxoplasmata recovered from the tissues of necropsied birds killed mice even in the first passage on or about the fifth day. Intracerebral inoculation of both strains into 1-week-old chicks

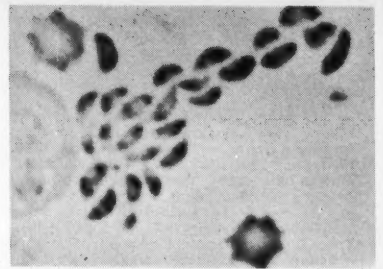


Fig. 3. Extracellular forms in the impression smear of peritoneal exudate of mice. Note the crenated erythrocytes (phase-contrast $\times 1500$). [May-Grunwald-Giemsa]

brought about their death with encephalitis in about 72 hours, while 10-week-old chicks that received heavy inocula by the subcutaneous route showed only mild transient parasitaemia and survived exposure. All the strains killed the embryos of 7-day-old embryonating eggs when they were inoculated directly into the yolk sac.

The susceptibility of embryonating hen's eggs to experimental infection with toxoplasma was established quite early (4), and today the chick embryo is considered to be the only available host in which parasites of low virulence can be maintained (5). But no natural infections have been previously described.

This is evidently the first report on the occurrence of toxoplasma in hen's eggs where a definite identification has been accomplished by morphological, serological, and animal recovery tests. Our data support the hypothesis that raw eggs could serve as sources of infections for human beings. This aspect of avian toxoplasmosis needs urgent and immediate attention; such an investigation is already in progress at this laboratory.

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21 September 1960

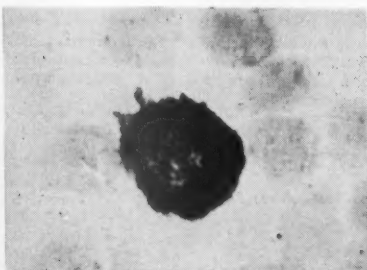


Fig. 1. Cyst stages of *Toxoplasma gondii* in the impression smear of chorioallantoic membrane. Note the absence of nuclei in the cyst wall (about $\times 1000$). [Giemsa]

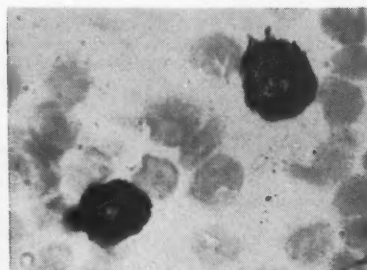
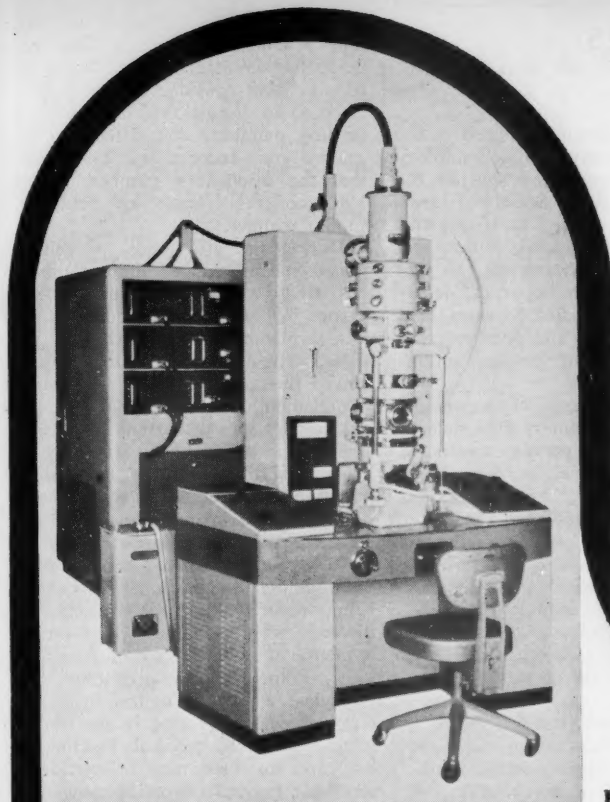


Fig. 2. Pseudocyst of *Toxoplasma* in the ovary of white Leghorn hen. Note the size that varies between 50 to 100 μ (about $\times 1000$). [Giemsa]

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Meetings

Bioclimatology

The second scientific congress of the International Society of Bioclimatology and Biometeorology was held in the chambers of the Royal Society of Medicine, in London, from 5 to 10 September 1960. There were 172 members attending, from 26 countries. The program represented an important departure from that of the first congress (held in Vienna in 1957), and perhaps from programs of most other national and international societies.

Productive exchange of viewpoints within an interdisciplinary field such as bioclimatology is not greatly encouraged by marathons of brief technical communications. Rather, lively discussion of basic concepts, problems, and methodology leads to important cross-fertilization and growth of ideas. To this end, the executive board designed a program aimed at stimulating discussion both on broad problems and on technical matters. On each of four mornings a basic theme was discussed by three speakers, each representing a different background. The speakers were instructed to concentrate on major unsettled issues and their possible resolution. One or several moderators then initiated discussion of the themes and suggestions raised by the main speakers.

The subjects of these four sessions and the speakers were as follows:

1) "High-altitude Bioclimatology": R. Margaria (University of Milan), W. H. Weihe (University of Bern), and R. Schindler (Bernhard-Nocht-Institut, Hamburg).

2) "Tropical Bioclimatology": A. B. Hertzmann (St. Louis University School of Medicine), J. C. D. Hutchinson (Ian Clunies Ross Animal Research Laboratory, Parramatta, Australia), P. W. Richards (University College of North Wales), and C. P. Luck (Kampala, Uganda).

3) "Bioclimatological Classifications": H. Boyko (Negev Institute for Arid Zone Research, Beersheva, Israel), K. J. K. Buettner (University of Washington, Seattle), and H. Juszat (Heidelberger Akademie der Wissenschaften).

4) "Meteoro-pathological Forecasting": P. M. A. Bourke (Irish Meteorological Service), M. Crawford (Commonwealth Bureau of Animal Health, Great Britain), and Frederick Sargent, II (University of Illinois).

As might have been anticipated, the sessions were not uniformly successful. General discussion was frequently limited because there were too many moderators and because the moderators gave their own views instead of leading the discussion. When these problems

were avoided, the discussion was lively and productive. Provision had been made for simultaneous translation, and this gave a considerable measure of freedom in discussion. Most of the attending members considered the program a great success, and it was voted that the discussions planned for the 1963 congress should be held in a similar manner.

During the afternoons, participants joined specialized working groups on restricted technical subjects. These groups worked under a moderator, and few formal communications were presented. The members of the groups discussed their own work and attempted to define both the problems and the general implications of current advances in their special areas. In this way they discussed thermoregulation; atmospheric pollution and aerobiology; agrometeorology; the effects of weather and climate on cattle; urban and architectural climatology; the importance of physical environment in conditioning the organism; microclimatic problems; allergic diseases, with special emphasis on the influence of climate on bronchial asthma; ecological climatography; the biological effects of ionization of the air; chemical tests used in bioclimatological research; tropical bioclimatology; and solar radiation in relation to bioclimatology. These discussions were highly successful and will be continued during future meetings.

The scientific caliber of the formal presentations and the discussions was refreshingly high, and there was a distinctly experimental note. The membership seemed ready to come to grips with mesological mechanisms rather than indulge in speculations arising from chance bioclimatological relationships. In particular, the discussion of human bioclimatology was stimulating and sound.

At the business meeting the following executive board was elected: president, F. Sargent, II (United States); vice presidents, M. P. A. Bourke (Ireland), H. Boyke (Israel), and M. Fontaine (France); advisory members, J. L. Cloudsey-Thompson (Sudan) and W. G. Wellington (Canada); and secretary-treasurer, S. W. Tromp (Netherlands). At the business meeting it was also decided that in future the *Journal of Bioclimatology* will be devoted to reviews. There is a great need for critical appraisals of many aspects of bioclimatology, and no current periodical deals extensively with this important field. It was further decided that a publications committee should explore ways of working with abstracting services and in other ways attempt to provide greater access to the diverse literature of the field.

The proceedings of the congress will

be published in book form by Pergamon Press. They will be available early in 1961 at a cost of approximately \$10, either from the secretariat of the society at Hofbrouckerlaan 54, Oegstgeest (Leiden), Netherlands, or from the publisher.

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WALTER R. HENSON
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New Haven, Connecticut

Forthcoming Events

March

24-29. National Science Teachers Assoc., Chicago, Ill. (R. H. Carleton, NSTA, 1201 16th St., NW, Washington 6)

26-29. American Assoc. of Dental Schools, annual, Boston, Mass. (R. H. Sullens, 840 N. Lake Shore Dr., Chicago 11, Ill.)

27-31. Temperature—Its Measurement and Control in Science and Industry, natl. symp., Columbus, Ohio. (C. M. Herzfeld, National Bureau of Standards, Washington 25, D.C.)

30-1. Southern Soc. for Philosophy and Psychology, Atlanta, Ga. (D. R. Kenshalo, Dept. of Psychology, Florida State Univ., Tallahassee)

April

3-6. Massachusetts Institute of Technology, centennial celebration, Cambridge. (Office of Public Relations, M.I.T., Cambridge 39)

3-15. Medical Conference, 11th, Nassau, Bahamas. (Bahamas Conferences, P.O. Box 1454, Nassau)

4-6. Electromagnetics and Fluid Dynamics of Gaseous Plasma, intern. symp., New York, N.Y. (J. Fox, Microwave Research Inst., Brooklyn 1, N.Y.)

4-7. Society of Automotive Engineers, natl. aeronautic meeting, New York, N.Y. (E. W. Conlon and G. W. Periman, 485 Lexington Ave., New York 17)

4-8. National Council of Teachers of Mathematics, 39th annual, Chicago, Ill. (F. A. Janacek, J. S. Morton High School, Cicero 50, Ill.)

5-8. Water Relations of Plants, British Ecological Soc., symp., London. (F. H. Whitehead, Botany Department, Imperial College, Prince Consort Road, London, S.W.7)

6-7. Council on Medical Television, annual, Bethesda, Md. (Institute for Advancement of Medical Communication, 33 E. 68 St., New York 21)

7-8. Eastern Psychological Association, Philadelphia, Pa. (C. H. Rush, P.O. Box 252, Glenbrook, Conn.)

7-9. American Assoc. for Cancer Research, 52nd annual, Atlantic City, N.J. (H. J. Creech, Secretary-Treasurer, Inst. for Cancer Research, Fox Chase, Philadelphia 11, Pa.)

7-9. Fleming's Lysozyme, 2nd intern. symp., Milan, Italy. (R. Ferrari, Organizing Committee, Via Modica 6, Milan)

8-9. Histochemical Soc., 12th annual, Atlantic City, N.J. (H. W. Deane, Albert

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Einstein College of Medicine, Bronx 61, N.Y.)

9-13. American Assoc. of Cereal Chemists, annual, Dallas, Tex. (J. W. Pence, Western Utilization Research & Development Division, 800 Buchanan St., Albany 10, Calif.)

9-13. American Industrial Hygiene Assoc., Detroit, Mich. (W. S. Johnson, Bethlehem Steel Co., Bethlehem, Pa.)

9-15. American Institute of Nutrition, Atlantic City, N.J. (A. E. Schaefer, ICNND, Bldg. 16A, National Institutes of Health, Bethesda 14, Md.)

10-14. American Soc. of Civil Engineers, Phoenix, Ariz. (W. H. Wisely, 33 W. 39 St., New York 18)

10-14. Detection and Use of Tritium in the Physical and Biological Sciences, intern. symp., Vienna, Austria. (Office of Special Projects, U.S. Atomic Energy Commission, Washington 25, D.C.)

10-15. Federation of American Societies for Experimental Biology, 45th annual, Atlantic City, N.J. (M. O. Lee, 9650 Wisconsin Ave., Washington 14, D.C.)

10-15. Metallic Corrosion, 1st intern. cong., London, England. (Society of Chemical Industry, 14 Belgrave Sq., London, S.W.1)

11-13. Institute of Environmental Sciences, annual, Chicago, Ill. (H. Sanders, Box 191, Mt. Prospect, Ill.)

11-13. Ultrapurification of Semiconductor Materials, conf., A.F. Office of Scientific Research, Boston, Mass. (Miss H. Turin, Conf. Secretary, Electronics Research Directorate, Air Force Cambridge

Research Lab., L. G. Hansom Field, Bedford, Mass.)

12-13. Information and Decision Processes, 3rd symp., Lafayette, Ind. (R. E. Machol, School of Electrical Engineering, Purdue Univ., Lafayette)

12-14. Agglomeration, intern. symp., Philadelphia, Pa. (Metallurgical Soc. of the AIME, 29 W. 39 St., New York 18)

12-14. Chemical Soc., anniversary meeting, Liverpool, England. (Chemical Society, Burlington House, Piccadilly, London, W.1)

13-14. Society of Technical Writers and Publishers, 8th annual, San Francisco, Calif. (R. B. Meier, Head Editor, Engineering, Stanford Research Inst., 333 Ravenswood Ave., Menlo Park, Calif.)

17-18. Great Lakes Research, 4th conf., Ann Arbor, Mich. (C. F. Powers, Great Lakes Research Division, 1119 Natural Science Bldg., Ann Arbor)

17-19. Fluid Seal Meeting, intern., Ashford, Kent, England. (Information Officer, British Hydromechanics Research Assoc., South Road, Temple Fields, Harlow, Essex)

17-24. International Congress of Nurses, 12th quadrennial cong., Melbourne, Australia. (Miss D. C. Bridges, Secretary, 1 Dean Trench Street, London, S.W.1, England)

18-20. Chemical Reactions in the Lower and Upper Atmosphere, intern. symp., San Francisco, Calif. (R. D. Cadle, Stanford Research Inst., Menlo Park, Calif.)

18-21. American Geophysical Union and American Meteorological Soc., Wash-

ington, D.C. (American Geophysical Union, 1515 Massachusetts Ave., NW, Washington 5, D.C.)

19-21. Southwestern Inst. of Radio Engineers Conf. and Electronics Show, Dallas, Tex. (SWIRECO 61, P.O. Box 7443, Dallas 9)

20-21. Society of Chemical Industry, fungicide symp., London, England. (B. J. Heywood, 103 Harrow Drive, Hornchurch, Essex, England)

20-22. Association of Southeastern Biologists, Lexington, Ky. (H. J. Humm, Department of Botany, Duke Univ., Durham, N.C.)

20-24. Microbial Reactions in Marine Environments, intern. symp., Chicago, Ill. (C. H. Oppenheimer, Inst. of Marine Science, Univ. of Texas, Port Arkansas)

21-22. American Assoc. of Univ. Professors, Boston, Mass. (W. P. Fidler, AAUP, 1785 Massachusetts Ave., NW, Washington 6, D.C.)

23. American Pharmaceutical Assoc., Chicago, Ill. (W. S. Apple, 2215 Constitution Ave., NW, Washington, D.C.)

23-26. American Assoc. of Colleges of Pharmacy, Chicago, Ill. (C. W. Bliven, George Washington Univ., Washington 6, D.C.)

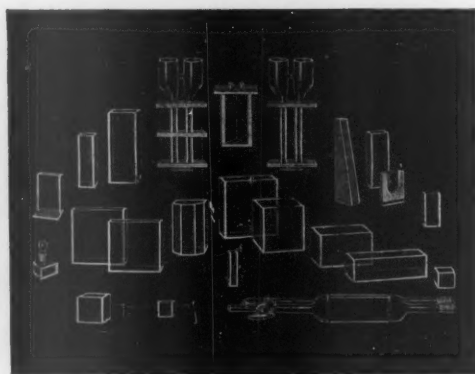
23-27. American Ceramic Soc., 63rd annual, Toronto, Canada. (C. S. Pearce, 4055 N. High St., Columbus 14, Ohio)

23-27. Society of American Bacteriologists, Chicago, Ill. (E. M. Foster, 311 Bacteriology, Univ. of Wisconsin, Madison)

(See issue of 17 February for comprehensive list)

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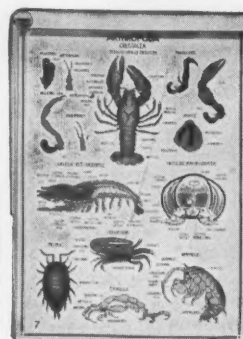


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Letters

Fell Swoop

With Tom Brown safely underground for some 250-odd years, perhaps one may be allowed to adapt his famous lines, and to thank Honor B. Fell for her delightful "Fashion in cell biology" [*Science* 132, 1625 (1960)] as follows:

Well do I like thee, Dr. Fell,
The reason why I fain would tell;
Since fads in cells thou dost dispel,
Well do I like thee, Dr. Fell.

F. B. HUTT

Department of Poultry Husbandry,
Cornell University, Ithaca, New York

Statistics and Legalized Gambling

Your 23 December issue [*Science* 132, 1859 (1960)] contained an excellent editorial on the value of properly weighted and applied statistical evidence. Thornton Page had an article, "Recent statistical studies in astronomy" [132, 1870 (1960)] which illustrated fine use of the method.

Unfortunately, there appeared in the same issue [132, 1879 (1960)] a prime example of the ignorant and careless use of statistics, a news note entitled, "... More is spent on [legalized] gambling than education," which included a statement by the "Council for Financial Aid to Education" to the effect that Americans spend \$20 billion a year for legalized gambling while only \$4.5 billion goes for higher education, the \$4.5 representing only half the actual cost, the other half being found in various ways by the institutions.

Neither your editor nor the council, in their zeal for drama, caught the falsity of the figures and their statistical misuse.

1) At least 90 percent of legalized gambling is on horse racing, on which there was a turnover of \$1 billion in New York and no more than a total of \$2.5 billion for the whole country.

2) This money is not all "spent"; 85 percent goes back to the bettors. Even if \$4 billion were bet, all but \$600 million is retained by the public. Of the \$600 million, about \$350 million goes for state taxes, some of which is used for higher education. The remaining \$250 million goes for upkeep of the tracks and for salaries and purses, and much of it is subject to federal income tax, a fraction of which is included in university grants.

Racing is conducted on a nonprofit basis at all New York tracks—Delaware, Aksarben, Fairgrounds, and Keeneland. The profits are donated for higher education, research, and civic

causes. Many more millions are donated each year for the same purposes by the profit-making tracks. Racing and breeding provide employment for thousands who pay taxes to keep the wheels turning.

What did the council mean by "spent" money? Did they mean wasted money? Does anyone really know about "money"? On any basis, higher education does not suffer because of legalized gambling. If all money were put into education and the mere raising of potatoes (production of essentials), we would have the Puritan New England of 1750 (and about 60 percent of our people would be out of work).

Ordinary gambling needs no justification. Those who live in the world of reality realize that it is an established human urge and that even a small wager provides a bit of romance, however fleeting, in the drab life of millions of people.

The majority of the faculty members of our universities are well informed, but all professors are not necessarily intellectuals, and all scientists are not educated, as was readily admitted in his own defense by J. Robert Oppenheimer.

Fortunately we have only a few who deserve to be called eggheads and who would have made the mistake on gambling statistics. However, when they appear they are as conspicuous as the rare drunken son of a religious leader.

More and more academicians are in the spotlight, and more is expected from them than from any other group. Scientists, previously silent, are now articulate (sometimes vociferous) on public matters, and Kennedy has gone to the universities for many high-ranking appointments (and good ones).

For the sake of the students and of the nation, we hope for our educators and scientists a complete education in the "humanities," meaning not only the proper university disciplines but also the humanities of the world at large—knowledge of things in general and of the facts of life.

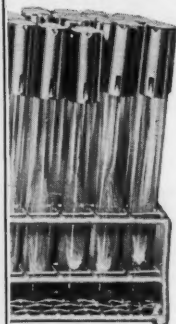
ESLIE ASBURY

902 Carew Tower, Cincinnati, Ohio

Naming Enzymes

Enzymes are usually named after the substrate used by the investigators who first describe them. The name is not necessarily stable, because further work may show that other substrates are attacked. For instance, tyramine oxidase is now called monaminooxidase because many amines besides tyramine are oxidatively deaminated by the enzyme. Such a change in name is desirable, as is any change which defines more precisely the activity of the enzyme.

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TAS/RC. 56

These considerations are promoted by the following case history. Some years ago my co-workers and I described and partially purified an enzyme found in some plants and animals which hydrolyzes hydantoin to hydantoic acid [*J. Biol. Chem.* **163**, 683 (1946); **181**, 449 (1949)]. Since no substituted hydantoins were hydrolyzed, the name hydantoinase seemed appropriate. The enzyme is very active but its function is not clear, since nobody has been able to bring unsubstituted hydantoin into any metabolic scheme. This is always somewhat frustrating.

In 1957, Wallach and Grisolia [*J. Biol. Chem.* **226**, 277 (1957)] further

purified the enzyme, which they said we called hydantoin peptidase—a name we had not thought of. This preparation, which was 80-percent pure, hydrolyzed hydropyrimidines as well as hydantoin. They renamed the enzyme hydropyrimidine hydrazase, and Dixon and Webb [*Enzymes* (Academic Press, New York, 1958)] rapidly made a further contribution by calling it dihydropyrimidinase.

The enzyme now has a respectability it did not have as a simple hydantoinase, since everyone is interested in pyrimidines and nobody in hydantoin. But, as Wallach and Grisolia showed, the turnover number for hy-

dantoin is 27,000; for hydouracil, 4300; and for hydrothymine, 420. The K_m for hydantoin is higher than the K_m for the pyrimidines, but these values have not been used as criteria for naming enzymes.

The question is this: Does one name an enzyme after the substrate most rapidly attacked, or after the substrate of most interest? Apparently the latter. One is reminded that some years ago certain towns in Russia changed names in accordance with the current political status of the leaders. Perhaps enzymes should be named in accordance with the current metabolic status of the substrates.

F. BERNHEIM

Duke University Medical Center,
Durham, North Carolina

Advancement of Scientists

Please accept my resignation from the AAAS in protest of your policy, which, in my opinion, fails to advance science because of your reluctance to aggressively push for the advancement of *scientists*. I am not denying that you do a good job in disseminating the facts of science, and you may even encourage a certain amount of research. But the fact remains that science will only really be advanced when the scientist himself has gained greater status, more recognition, and more acceptance by the average American as someone to look up to. The American Medical Association has accomplished this for physicians in the United States. What we need is a comparable association that will achieve this for America's Ph.D. scientists.

Whether or not you like this approach, or whether you feel that it goes against the grain of your organization to compromise the scientific ivory-tower tradition, the fact remains that the Ph.D. scientist is not generally compensated in our culture for the sacrifice, effort, and skill that his extensive training entails. I don't like the idea of unions being necessary, but if it takes a "union" (such as the AMA) to get the scientist his due, then any organization dedicated to the advancement of science must transform itself into a union.

My resignation is predicated on the fact that I believe that it is a hopeless task to try to influence the AAAS in regard to its obligation to the scientists. This is not the first correspondence I have had with your office on this subject. Therefore, I feel that I must resign. As a final request I will ask you to print this letter in *Science*.

THEODORE C. KAHN

United States Air Force Hospital,
Wiesbaden, Germany

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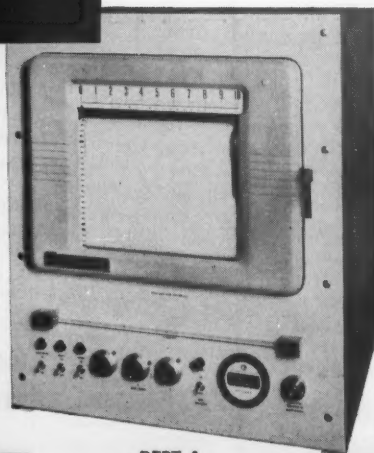
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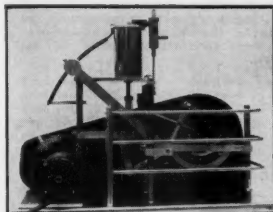
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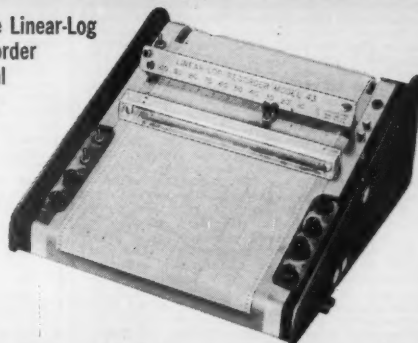
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on page 610

Tissue Culture Course

The annual course in Principles and Techniques of Tissue Culture sponsored by the Tissue Culture Association will be given at the University of Wisconsin, Madison, Wisconsin, 19 June to 14 July 1961. A limited number of participants (post-doctoral research workers and teachers) can be admitted. The course will be directed by Dr. JOHN PAUL of Glasgow University and Dr. WILLIAM G. COOPER of the University of Colorado School of Medicine. For further information and application forms, address Dr. Mary S. Parshley, College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York. Tuition \$100. Deadline for application, 15 April 1961.

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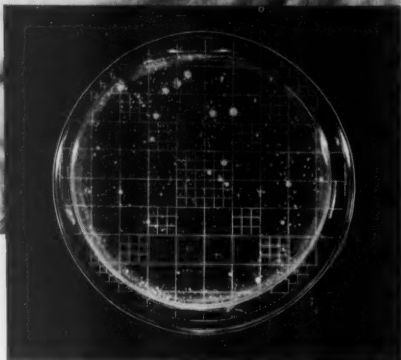
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